Table 7.19. Serious Adverse Events that Led to Discontinuation RT Population

	Number of Patients with an Event Regardless of Drug Causality		Number of Patients with an Event Possibly Drug Related	
Reason	LY/cis (N=226)	Cisplatin (N=222)	LY/cis (N=226)	Cisplatin (N=222)
Cerebral ischemia	2 (0.9%)	0	0	0
Diarrhea	2 (0.9)	0	2 (0.9%)	0
Anemia	1 (0.4)	0	1 (0.4)	0
Blood creatinine increased	1 (0.4)	0	1 (0.4)	0
Vomiting	1 (0.4)	0	1 (0.4)	0
Angina pectoris	1 (0.4)	0	1 (0.4)	0
Atrial fibrillation	1 (0.4)	0	0	0
Condition aggravated	1 (0.4)	0	1 (0.4)	0
Depression	1 (0.4)	0	0	0
Pulmonary embolism	1 (0.4)	0	1 (0.4)	0
Tumor pain	1 (0.4)	0	0	0
WBC decreased	1 (0.4)	0	1 (0.4)	0
Hypertension NOS	1 (0.4)	0	0	0
Cardiac failure	0	1 (0.5%)	0	1 (0.5%)
Dehydration	0	1 (0.5)	0	0
Fluid overload	0	1 (0.5)	0	0
Jugular vein thrombosis	0	1 (0.5)	0	0
Right ventricular failure	0	1 (0.5)	0	1 (0.5)
Total	15 (6.6)	5 (2.3)	9 (4.0)	2 (0.9)

Source: Applicant Table JMCH.12.26.

A nonserious clinically significant event was defined as any non- serious adverse event that led to discontinuation from the study. Thirteen patients discontinued on both the Alimta/ cisplatin arm as well as the cisplatin alone arm. In both treatment arms, the most frequent reason for discontinuation was decreased creatinine clearance (7 [3.1%] on the Alimta/ cisplatin arm, 9 [4.1%] on the cisplatin alone arm). A decrease in creatinine clearance was the only event occurring in > 1% of patients, occurring with similar frequency (3.1% versus 3.6%) in the two arms. Table 7.20 summarizes these patient discontinuations.

Table 7.21 shows the number of patients discontinuing treatment for grade 3/4 toxicity in each treatment group.

Table 7.20. Discontinuations Because of Nonserious, Clinically Significant Adverse Events RT Population

	Number of Patients with an Event Regardless of Drug Causality		Number of Patients with an Event Possibly Drug Related	
Reason	LY/cis (N=226)	Cisplatin (N=222)	LY/cis (N=226)	Cisplatin (N=222)
CrCl decreased	7 (3.1%)	9 (4.1%)	7 (3.1%)	8 (3.6%)
Anemia	1 (0.4)	0	1 (0.4)	0
Deafness	1 (0.4)	0	1 (0.4)	0
Nausea	1 (0.4)	0	1 (0.4)	0
Neuropathy NOS	1 (0.4)	0	1 (0.4)	0
Vomiting	1 (0.4)	0	1 (0.4)	0
Pneumonitis NOS	1 (0.4)	0	1 (0.4)	0
Fatigue	0	1 (0.5)	0	1 (0.5)
Hypoasthesia	0	1 (0.5)	0	1 (0.5)
Tinnitus	0	1 (0.5)	0	1 (0.5)
Weight decreased	0	1 (0.5)	0	0
Total	13 (5.8)	13 (5.9)	13 (5.8)	11 (5.0)

Source: Section 12.3.1.2. Applicant Table JMCH 12.27.

Table 7.21. Discontinuations for Grade 3/4 AE (Reviewer's Table)

Adverse Events	No. of patients with each AE							
	RT population				Fully Supplemented			
	Alimta/Cisplatin		Cisplatin		Alimta/Cisplatin		Cisplatin	
	N	%	N	%	N	%	N	%
Leukocytes	8	3.5	0	0	4	2.4	0	0
Fatigue	5	2.2	1	0.5	4	2.4	1	0.6
Dyspnea	4	1.8	5	2.3	4	2.4	5	3.1
Neutrophils/granulocytes	9	4.0	0	0	3	1.8	0	0
Nausea	6	2.7	1	0.5	3	1.8	1	0.6
Vomiting	6	2.7	0	0	3	1.8	0	0
Platelets	4	1.8	0	0	2	1.2	0	0
Chest pain	2	0.9	3	1.4	2	1.2	3	1.8
Hypertension	2	0.9	4	1.8	2	1.2	4	2.5
Renal/Genitourinary-Other	2	0.9	1	0.5	2	1.2	1	0.6

Adverse Events	No. of patients with each AE							
	RT population				Fully Supplemented			
	Alimta/Cisplatin		Cisplatin		Alimta/Cisplatin		Cisplatin	
	N	%	N	%	N	%	N	%
Hemoglobin	3	1.3	0	0	1	0.6	0	0
Constitutional Symptoms-Other	2	0.9	0	0	1	0.6	0	0
Cushingoid appearance	1	0.4	0	0	1	0.6	0	0
Dehydration	1	0.4	1	0.5	1	0.6	1	0.6
Hypokalemia	1	0.4	0	0	1	0.6	0	0
Mood alteration-anxiety agitation	1	0.4	0	0	1	0.6	0	0
Mood alteration-depression	1	0.4	0	0	1	0.6	0	0
Other cardiovascular/arrhythmia	1	0.4	0	0	1	0.6	0	0
Other cardiovascular/general	1	0.4	1	0.5	1	0.6	1	0.6
Pulmonary-Other	1	0.4	1	0.5	1	0.6	1	0.6
Supraventricular arrhythmias	1	0.4	0	0	1	0.6	0	0
Thrombosis/embolism	1	0.4	1	0.5	1	0.6	1	0.6
Tumor pain	1	0.4	0	0	1	0.6	0	0
CNS Cerebrovascular ischemia	2	0.9	0	0	0	0	0	0
Diarrhea without colostomy	2	0.9	0	0	0	0	0	0
Abdominal pain or cramping	1	0.4	0	0	0	0	0	0
Alopecia	1	0.4	0	0	0	0	0	0
Fever	1	0.4	0	0	0	0	0	0
Hyperglycemia	1	0.4	2	0.9	0	0	2	1.2
Hypoglycemia	1	0.4	0	0	0	0	0	0
Inner ear/hearing	1	0.4	0	0	0	0	0	0
Other auditory/hearing	1	0.4	0	0	0	0	0	0
Other endocrine	1	0.4	0	0	0	0	0	0
Other neurology	1	0.4	0	0	0	0	0	0
Syncope	1	0.4	0	0	0	0	0	0

3.3 Deaths

Among patients who were randomized and treated, 22 died while on study or within 30 days of end of study or discontinuation, 14 of whom had been treated with Alimta/ cisplatin and 8 with cisplatin alone. Eight deaths in the Alimta/ cisplatin arm and three in the cisplatin alone arm occurred in the first two cycles of therapy and five deaths in the Alimta/ cisplatin arm and three in the cisplatin alone arm occurred in the 30 days following the last infusion of study drug. The on-study death rates in the RT group were 6.2% in the Alimta/cisplatin arm and 3.6% in the cisplatin alone arm.

In the FS subgroups, the death-rates were 4.8% in the Alimta/cisplatin arm and 3.7% in the cisplatin alone arm.

Tables 7.22 and 7.23 summarize deaths that occurred while patients were on-study. The deaths were fewer in the Alimta/cisplatin arm of the FS group.

Table 7.22. Summary of on- study Deaths RT Population

Reasons for Death	LY/cis (N=226)	Cisplatin (N=222)
Study Drug Toxicity		
Febrile neutropenia	1 (0.4%)	0
Study Disease		
Study disease[1]	11 (4.9)	5 (2.3%)
Other Causes		
Cerebrovascular accident NOS	1 (0.4)	0
Myocardial infarction	0	1 (0.5)
Septic shock	1 (0.4)	0
Sudden death unexplained	0	1 (0.5)
Thrombosis NOS	0	1 (0.5)
Total	14 (6.2)	8 (3.6)

[1] Two of the 11 deaths on the LY/cis arm are considered to be study disease-related by investigators, but were considered to be possibly study drug-related, in the opinion of the Lilly physician.

Source: Section 12.3.1.1. Applicant Table JMCH. 12.21.

Table 7.23. Summary of on- study Deaths RT Population by Supplementation Status

	LY/cis		Cisplatin	
Reason	FS (N=168)	PS+NS (N=58)	FS (N=163)	PS+NS (N=59)
Study Drug Toxicity				
Febrile neutropenia	0	1 (1.7%)	0	0
Study Disease				
Study disease[1]	6 (3.6%)	5 (8.6)	4 (2.5%)	1 (1.7%)
Other Causes				
Cerebrovascular accident NOS	1 (0.6)	0	0	0
Myocardial infarction	0	0	0	1 (1.7)
Septic shock	1 (0.6)	0	0	0
Sudden death unexplained	0	0	1 (0.6)	0
Thrombosis NOS	0	0	1 (0.6)	0
Total	8 (4.8)	6 (10.3)	6 (3.7)	2 (3.4)

[1] Two of the 6 deaths on the LY/cis arm are considered to be study disease-related by investigators, but were considered to be possibly study drug-related, in the opinion of the Lilly physician.

Source: Section 12.3.1.1. Applicant Table JMCH 12.22.

Only one on-study death was thought by investigators to be possibly related to study drug (patient 510-5100). However, the symptoms leading to two other deaths warranted a closer examination of the circumstances. All cases discussed below were reviewed from the applicant's death summary and CRF.

Patient 510- 5100 (on the Alimta/ cisplatin arm and never supplemented) was a 75-year male diagnosed with stage IV epithelial MPM scar lesions and cranial and chest lymph nodes. The patient had undergone decortication and pleurectomy in June 1998. His KPS score was 90 with dyspnea on exertion as the only symptom. He started the first treatment of Alimta/cisplatin on 16 June 1999 and the last infusion was on 26 July 1999. He completed two cycles of therapy. Side effects in cycle 1 were CTC grade 1 rash, fever, nausea, anorexia, fatigue, and grade 3 neutropenia, leukopenia and thrombocytopenia. Cycle 2 was delayed because of poor appetite and generally feeling unwell. A blood transfusion was given because of low levels of hemoglobin on 26 July in cycle 2. The patient was seen in a clinic on day 8. He complained of grade 1 nausea but appeared well. One week later the patient's general practitioner informed the investigator that the patient had experienced fever, diarrhea, and stomatitis 13 days after the last dose of study drug. He was given morphine and had planned to come to the hospital the next day. He died at home on 09 August 1999. An autopsy was not performed.

Patient 214-2148 (Alimta/cisplatin arm, supplemented) was a 58-year old male with stage IV mixed cell MPM who was randomly assigned to receive Alimta/cisplatin and received only one cycle on 02 February 2000. On [redacted] he was hospitalized for stomatitis and anorexia. A chest x-ray did not show disease progression. His condition worsened and he died on [redacted]. An autopsy was not performed. Although the investigator felt that the study drug was not related to his death, a relationship to study drug cannot be completely excluded.

Patient 804-8040 (Alimta/cisplatin, never supplemented) was a 59-year old male with Stage IV mixed cell MPM randomly assigned to receive Alimta/cisplatin. He received one cycle on 08 September 1999. Three days later, he experienced grade 3 nausea, vomiting, exertional dyspnea as well as grade 4 febrile neutropenia, leukocytes and neutrophils and died on 16 September 1999. An autopsy was not performed. A relationship to study drug cannot be excluded.

The cause of death in all other patients could be attributed to the underlying disease or to complications thereof.

Reviewers comment:
According to the sponsor and investigator, only one death was due to study drug toxicity. However, based on the above, 3 deaths in patients treated with Alimta/cislatin were possibly treatment related, the common thread being febrile neutropenia.
One death occurred in the Alimta/cisplatin arm with vitamin supplementation.

3.4 Serious, Unexpected, Reportable Adverse Events

Serious, unexpected, reportable adverse events were those events that were not described or listed in the clinical investigator's brochure and considered by the investigator or sponsor to be possibly or probably related to the study drug. Table 7.24 details these events.

Six patients on the Alimta/ cisplatin arm and 3 patients on the cisplatin alone arm experienced a serious, unexpected, reportable event. Except for constipation, all events were unique to a specific patient. Two events, ulcerative esophagitis and death, were attributable to Alimta.

Table 7.24. Serious, Unexpected, Reportable Adverse Events RT Population

LY/cis N=226				Cisplatin N=222			
Patient Number	FS/PS+NS	Drug Associated	Event	Patient Number	FS/PS+NS	Drug Associated	Event
101-1018	FS	Cisplatin	Hypovolemia	136-1632	FS	Cisplatin	Urinary retention
130-1196	FS	Cisplatin	Polyneuropathy	409-4178	FS	Cisplatin	Subileus and constipation
141-1461	FS	LY/cis	Ulcerative esophagitis	720-7208	FS	Cisplatin	Headache
216-2161	PS+NS	Cisplatin	Constipation				
510-5100	PS+NS	LY/cis	Death[1]				
554-5516	FS	Cisplatin	Angina pectoris				

[1] This patient death was possibly related to other events such as diarrhea, stomatitis, and fever that are associated with LY231514 therapy.

Source: Sponsors Table JMCH.12.28.

3.5 Hospitalizations

In the RT population, 100 patients were hospitalized, 67 in the Alimta/cisplatin arm and 33 in the cisplatin alone arm. In the FS population, 67 patients were hospitalized, 46 in the Alimta/cisplatin arm and 21 in the cisplatin alone arm. More patients were hospitalized in the Alimta/cisplatin arm than the cisplatin alone arm.

Table 7.25 details the common reasons for hospitalization. The most common reasons were neutropenia, febrile neutropenia, infection, decreased renal function, stomatitis, nausea, vomiting, fatigue and diarrhea.

Table 7.25. Most Common Reasons for Hospitalization (Reviewers Table)

Reason for Hospitalization	No. of patients with each event							
	RT population				Fully Supplemented			
	Alimta/Cisplatin		Cisplatin		Alimta/Cisplatin		Cisplatin	
	N	%	N	%	N	%	N	%
Neutrophil count decreased	67	29.6	33	14.9	46	27.4	21	12.9
Febrile neutropenia	67	29.6	33	14.9	46	27.4	21	12.9
Infection NOS	67	29.6	33	14.9	46	27.4	21	12.9
Nausea	67	29.6	33	14.9	46	27.4	21	12.9
Blood creatinine increased	67	29.6	33	14.9	46	27.4	21	12.9
Creatinine renal clearance decreased	67	29.6	33	14.9	46	27.4	21	12.9
Fatigue	67	29.6	33	14.9	46	27.4	21	12.9
Diarrhoea NOS	67	29.6	33	14.9	46	27.4	21	12.9
Stomatitis	67	29.6	33	14.9	46	27.4	21	12.9
Vomiting NOS	67	29.6	33	14.9	46	27.4	21	12.9
White blood cell count decreased	67	29.6	32	14.4	46	27.4	21	12.9
Platelet count decreased	67	29.6	33	14.9	46	27.4	21	12.9
Pneumonitis NOS	67	29.6	33	14.9	46	27.4	21	12.9
Rash NOS	67	29.6	33	14.9	46	27.4	21	12.9
Alanine aminotransferase increased	67	29.6	33	14.9	46	27.4	21	12.9
Aspartate aminotransferase increased	67	29.6	33	14.9	46	27.4	21	12.9
Blood bilirubin increased	67	29.6	33	14.9	46	27.4	21	12.9
Dyspnoea NOS	49	21.7	28	12.6	35	20.8	18	11.0

	No. of patients with each event							
	RT population				Fully Supplemented			
	Alimta/Cisplatin		Cisplatin		Alimta/Cisplatin		Cisplatin	
Constipation	38	16.8	16	7.2	30	17.9	9	5.5
Cough	34	15.0	11	5.0	25	14.9	6	3.7
Anaemia NOS	27	11.9	6	2.7	21	12.5	4	2.5
Anorexia	25	11.1	9	4.1	16	9.5	3	1.8
Chest pain	19	8.4	10	4.5	15	8.9	7	4.3
Pyrexia	18	8.0	7	3.2	15	8.9	4	2.5
Hypertension NOS	19	8.4	8	3.6	14	8.3	5	3.1
Dehydration	19	8.4	1	0.5	12	7.1	1	0.6
Weight decreased	15	6.6	5	2.3	12	7.1	3	1.8
Tumour pain	12	5.3	4	1.8	10	6.0	1	0.6
Pulmonary embolism[1]	12	5.2	5	2.3	10	6.0	3	1.8
Anxiety NEC	9	4.0	6	2.7	8	4.8	2	1.2
Depression NOS	10	4.4	4	1.8	8	4.8	3	1.8
Oedema NOS	10	4.4	2	0.9	8	4.8	2	1.2
Oedema lower limb	9	4.0	5	2.3	8	4.8	3	1.8
Dizziness (excl vertigo)	8	3.5	2	0.9	6	3.6	2	1.2
Insomnia	9	4.0	6	2.7	6	3.6	3	1.8
Paraesthesia	6	2.7	1	0.5	6	3.6	1	0.6
Sweating increased	7	3.1	3	1.4	6	3.6	2	1.2
Breath sounds decreased	6	2.7	1	0.5	5	3.0	1	0.6
Diabetes mellitus NOS	8	3.5	3	1.4	5	3.0	3	1.8
Hypotension NOS	6	2.7	0	0.0	5	3.0	0	0.0
Pain NOS	13	5.8	7	3.2	5	3.0	4	2.5
Pleural effusion	5	2.2	0	0.0	5	3.0	0	0.0
Pleuritic pain	6	2.7	6	2.7	5	3.0	5	3.1
Weakness	7	3.1	3	1.4	5	3.0	2	1.2
Abdominal distension	4	1.8	1	0.5	4	2.4	1	0.6
Abdominal pain NOS	6	2.7	4	1.8	4	2.4	3	1.8
Renal events[2]	4	1.7	2	1.0	3	1.2	2	1.2

[1] includes pulmonary embolism, venous thrombosis, deep venous thrombosis, subclavian vein thrombosis, thrombosis

[2] Includes renal failure NOS, renal failure acute, renal impairment

3.6 Transfusions

On the Alimta/ cisplatin arm, 41 patients (18.1%) received a total of 138 units of red blood cell transfusions, two units of plasma transfusions, and four units of platelet transfusions, compared

with 17 patients (7.7%) on the cisplatin alone arm who received a total of 42 units of red blood cell transfusions and three units of plasma transfusions.
In the supplemented group, in both treatment arms, the incidence of red blood cell transfusions was lower among patients in the FS group when compared with the PS+ NS group. This supports data above showing a trend toward a lower incidence of grade 3/ 4 anemia in FS patients. The incidences of platelet and plasma transfusions were too low to justify any conclusions.

In the RT population, 19 (8.4%) patients used erythrocyte CSFs in those treated with Alimta/cisplatin while 5 (2.3%) patients used them in the cisplatin alone arm. In the supplemented subgroup, patients who used erythrocyte CSFs in the Alimta/cisplatin arm were 17 (10.1%) fully supplemented and 2 (3.4%) partially or never supplemented. In the cisplatin alone arm, 2 (1.2%) patients were fully supplemented and 3 (5.1%) were in the partially or never supplemented.

Table 7.26. Summary of Patients Who Received Transfusions On- study RT Population

Type of Transfusion	LY/cis (N=226)		Cisplatin (N=222)	
Patient with ≥1 Transfusion	41 (18.1%)		17 (7.7%)	
	Units	Patients	Units	Patients
RBC Transfusions	138	40 (17.7%)	42	16 (7.2%)
Platelet Transfusions	4	2 (0.9)	0	0
Plasma Transfusions	2	1 (0.4)	3	1 (0.5)

Patient could have received more than one type of transfusion.

Source: Section 12.5.2. Applicant Table JMCH.12.47

Table 7.27. Summary of patients Who received Transfusions On-Study RT population by Supplementation Status

	LY/cis				Cisplatin			
	FS		PS+NS		FS		PS+NS	
Type of Transfusion	(N=168)		(N=58)		(N=163)		(N=59)	
Patient with ≥1 Transfusion	26 (15.5%)		15 (25.9%)		11 (6.7%)		6 (10.2%)	
	Units	Patients	Units	Patients	Units	Patients	Units	Patients
RBC Transfusions	91	26 (15.5%)	47	14 (24.1%)	27	10 (6.1%)	15	6 (10.2%)
Platelet Transfusion	0	0	4	2 (3.4)	0	0	0	0
Plasma Transfusions	2	1 (0.6)	0	0	3	1 (0.6)	0	0

Patient could have received more than one type of transfusion.

Source: Section 12.5.2. Applicant Table JMCH.12.48.

Table 7.28. Summary of Reasons for Transfusions (Reviewers Table)

Reasons	RT Group				FS Subgroup			
	Alimta/cisplatin		Cisplatin		Alimta/cisplatin		Cisplatin	
	N	%	N	%	N	%	N	%
ANEMIA[1]	43	18.8	18	7.4	29	17.3	12	7.3
PLATELETS	2	0.9	0	0.0	0	0	0	0
DYSPNEA	1	0.4	0	0.0	1	0.6	0	0.0
FATIGUE	1	0.4	0	0.0	0	0	0	0
PROTHROMBIN TIME ELEVATED	1	0.4	0	0.0	1	0.6	0	0.0
SHORTNESS BREATH	1	0.4	0	0.0	0	0	0	0
LOW ALBUMIN	0	0.0	1	0.5	0	0.0	1	0.6

[1] Anemia and decreased hemoglobin have been combined.

3.7 Concomitant Drugs

The requirements for 5-HT_3 antagonists and other antiemetics did not change with the use of vitamin supplementation; however the use of anti-diarrheals decreased.

Table 7.29. Selected Concomitant Drug Therapy RT Population

	LY/cis (N=226)	Cisplatin (N=222)
Patients receiving at least 1 concomitant drug	226 (100%)	222 (100%)
Categories[1, 2]		
Corticosteroids (systemic)	224 (99.1)	221 (99.5)
5-HT_3 antagonists	215 (95.1)	211 (95.0)
Prokinetics (e.g., metoclopramide)	127 (56.2)	118 (53.2)
Other antiemetics (e.g., prochlorperazine)	86 (38.1)	67 (30.2)
H_2-antagonists	74 (32.7)	60 (27.0)
Proton pump inhibitors	66 (29.2)	46 (20.7)
Benzodiazepines	123 (54.4)	113 (50.9)
Morphine	60 (26.5)	43 (19.4)
Fentanyl	27 (11.9)	29 (13.1)
Codeine-containing products	58 (25.7)	51 (23.0)
Other narcotic-containing products	102 (45.1)	98 (44.1)
NSAIDs	86 (38.1)	79 (35.6)
Aspirin-containing products	35 (15.5)	32 (14.4)
Paracetamol-containing products	76 (33.6)	83 (37.4)
Anti-diarrheals	16 (7.1)	7 (3.2)
Erythrocyte colony-stimulating factors (CSFs)	19 (8.4)	5 (2.3)
Granulocyte CSFs	4 (1.8)	1 (0.5)
Folinic acid (leucovorin)	7 (3.1)	0

1 Patients may have taken more than one of the medications in the category.

2 Any particular drug product was only included in one category.

Source: Applicant Table JMCH. 11.16.

Table 7.30. Selected Concomitant Drug Therapy RT Population by Supplementation Status

	LY/cis		Cisplatin	
	FS (N=168)	PS+NS (N=58)	FS (N=163)	PS+NS (N=59)
Patients receiving at least 1 concomitant drug	168 (100%)	58 (100%)	163 (100%)	59 (100%)
Categories[1, 2]				
Corticosteroids (systemic)	166 (98.8)	58 (100)	162 (99.4)	59 (100)
5-HT_3 antagonists	160 (95.2)	55 (94.8)	157 (96.3)	54 (91.5)
Prokinetics (e.g., metoclopramide)	92 (54.8)	35 (60.3)	83 (50.9)	35 (59.3)
Other antiemetics (e.g., prochlorperazine)	64 (38.1)	22 (37.9)	46 (28.2)	21 (35.6)
H_2-antagonists	46 (27.4)	28 (48.3)	43 (26.4)	17 (28.8)
Proton pump inhibitors	49 (29.2)	17 (29.3)	35 (21.5)	11 (18.6)
Benzodiazepines	87 (51.8)	36 (62.1)	83 (50.9)	30 (50.8)
Morphine	43 (25.6)	17 (29.3)	31 (19.0)	12 (20.3)
Fentanyl	17 (10.1)	10 (17.2)	19 (11.7)	10 (16.9)
Codeine-containing products	41 (24.4)	17 (29.3)	36 (22.1)	15 (25.4)
Other narcotic-containing products	74 (44.0)	28 (48.3)	65 (39.9)	33 (55.9)
NSAIDs	59 (35.1)	27 (46.6)	59 (36.2)	20 (33.9)
Aspirin-containing products	22 (13.1)	13 (22.4)	22 (13.5)	10 (16.9)
Paracetamol-containing products	53 (31.5)	23 (39.7)	60 (36.8)	23 (39.0)
Anti-diarrheals	11 (6.5)	5 (8.6)	3 (1.8)	4 (6.8)
Erythrocyte colony-stimulating factors (CSFs)	17 (10.1)	2 (3.4)	2 (1.2)	3 (5.1)
Granulocyte CSFs	1 (0.6)	3 (5.2)	1 (0.6)	0
Folinic acid (leucovorin)	3 (1.8)	4 (6.9)	0	0

1 Patients may have taken more than one of the medications in the category.

2 Any particular drug product was only included in one category.

Source: Applicant Table JMCH. 11.17.

3.8 Supportive Studies

Table 7.31. Clinical Studies Discussed in the Integrated Summary of Safety

Study	Phase	Design	Status	Indication	No. Patients	Treatment[a]	Vitamin Suppl.	Dexamethasone Prophylaxis
LY231514 plus Cisplatin								
JMCH	3	Single-blind, randomized	Completed	MPM	Enrolled=456 Safety evaluable=448	LY231514, 500 mg/m^2 and cisplatin, 75 mg/m^2 vs cisplatin, 75 mg/m^2	Yes. 331 patients (both arms)	primary
JMAY	2	Open-label, nonrandomized	Completed	NSCLC	Enrolled=36 Safety evaluable=36	LY231514, 500 mg/m^2 and cisplatin, 75 mg/m^2	No	primary
JMBZ[b]	2	Open-label, nonrandomized	Completed	NSCLC	Enrolled=31 Safety evaluable=31	LY231514, 500 mg/m^2 and cisplatin, 75 mg/m^2	No	primary
JMAP	1	Open-label, dose-finding	Completed	Locally advanced or metastatic solid tumors	Enrolled=51 Safety evaluable=51	LY231514, 300 to 600 mg/m^2 plus Cisplatin, 60 to 100 mg/m^2	No	secondary
LY231514 Single-Agent Studies								
Integrated data on supplemented patients[c]	2	Open-label, nonrandomized	Completed	Breast and MPM	Enrolled=207 Safety evaluable=207	LY231514, 500 mg/m^2	Yes	primary
Integrated data on nonsupplemented patients[d]	2/3[h]	Open-label, randomized (JMBQ) and nonrandomized	Completed	Various cancers	Enrolled=608 Safety evaluable=608	LY231514, 500 and 600 mg/m^2, presented by starting dose	No	primary and secondary (specified per study in Table ISS.5.1)
Other – LY231514 Dose- and Schedule-Finding Studies								
JMAA	1	Open-label, dose-finding	Completed	Locally advanced or metastatic solid tumors	Enrolled=37 Safety evaluable=37	LY231514, 50 to 700 mg/m^2	No	none recommended
BP-001[f]	1	Open-label, dose-finding	Completed	Locally advanced or metastatic solid tumors	Enrolled=38 Safety evaluable=38	LY231514, 0.2 to 5.2 mg/m^2	No	none recommended
JMAB[g]	1	Open-label, dose-finding	Completed	Locally advanced or metastatic solid tumors	Enrolled=25 Safety evaluable=25	LY231514, 10 to 40 mg/m^2	No	none recommended

Abbreviations: AUC = area under the curve; MPM = malignant pleural mesothelioma; NSAIDs = nonsteroidal anti-inflammatory drugs; NSCLC = non-small cell lung cancer.

a One dose of the study drug(s) administered once every 21 days defined one cycle of therapy, unless otherwise noted.

b Studies conducted by the National Cancer Institute of Canada Clinical Trials Group (NCIC CTG). Data cannot be integrated with studies conducted by Lilly.

c Data from supplemented patients in studies JMBT, JMDM, JMDR, and JMDS.

d Data from nonsupplemented patients in studies JMAC, JMAD, JMAG, JMAH, JMAI, JMAJ, JMAK, JMAL, JMBB, JMBM, JMBP, JMBQ, JMBR, JMBT, JMDM, and JMDR.

e Supplementation regimen: 5 mg folic acid daily for 5 days beginning 2 days before each cycle; no vitamin B_{12} was given.

f A cycle was defined as LY231514 given daily for 5 days every 21 days.

g A cycle was defined as LY231514 given once per week for 28 days followed by a 14-day rest period.

h Three patients from a prematurely terminated Phase 3 study are included.

Source: Safety Update. Applicant Table 3.1.

Study JMDR

In the supporting Phase 2 study, Alimta was administered as a single agent to chemo-naïve patients with malignant pleural mesothelioma. The dose was 500 mg/m^2 given as an approximately 10- minute intravenous infusion on Day 1 of a 21- day period. This 21- day period defined one cycle of therapy. Dexamethasone, 4 mg (or an equivalent corticosteroid), was to be taken by all patients orally BID 1 day before, on the day of, and 1 day after the administration of Alimta.

Sixty- four patients were enrolled in the study. Forty- three patients were supplemented with folic acid and vitamin B_{12} and 21 were nonsupplemented.

The median age of patients at the time of enrollment was 65 years. The median age of supplemented patients was 63 years compared with 68 years for nonsupplemented patients.

All 64 patients received at least one cycle of Alimta. Enrolled patients completed a median of six cycles of therapy. The supplemented patients completed a median of six cycles and nonsupplemented patients completed a median of two cycles.

Three doses were reduced among the supplemented patients because of elevated febrile neutropenia, alkaline phosphatase levels and hypokinesia respectively. The adverse events that resulted in the four reductions among nonsupplemented patients were neutropenia (2 patients), febrile neutropenia, and stomatitis.

Nineteen dose delays occurred during the study. Thirteen delays occurred because of scheduling conflicts. Six were done for reasons that were considered clinically relevant. Five of these delays occurred in supplemented patients and were attributed to herpes zoster infection (2 patients), pain, asthenia, and myocardial infarction. A pleural disorder accounted for the single dose delay among the nonsupplemented patients.

All 64 patients were included in the safety analysis. Grade 3 or grade 4 neutropenia was reported in 15 patients. Eleven of these 15 patients were nonsupplemented and included 8 patients (38.1%) with grade 4 toxicity. Two supplemented patients (4.7%) reported grade 3 and 2 patients (4.7%) reported grade 4 neutropenia. Grade 3 or grade 4 leukopenia was reported in 12 patients. Eight of the 12 reports were in nonsupplemented patients, and included 2 patients (9.5%) with grade 4 toxicity. Four supplemented patients (9.3%) reported grade 3 leukopenia.

Fatigue and febrile neutropenia were the most commonly reported toxicities for nonlaboratory data. There were two reports each of these toxic events for supplemented and nonsupplemented patients. In general, the incidence of grade 4 toxicity was low for nonlaboratory data. Only one grade 4 event (chest pain) was reported in a nonsupplemented patient. In addition, ten grade 3 events were reported in 21 nonsupplemented patients, compared with fifteen grade 3 events in the 43 supplemented patients.

There were twenty- three reports of serious adverse events, thirteen among the nonsupplemented patients and ten among the supplemented patients. Fever (9 patients) was the most commonly reported overall. Fever in these 9 patients included five events reported verbatim as fever, three events of febrile neutropenia, and one event reported as fever without neutropenia. Fever was the most commonly reported SAE for supplemented patients. Six reports of fever included four events reported verbatim as fever, one as febrile neutropenia, and one as fever without neutropenia. Fever and leukopenia (three reports each) were most commonly reported serious adverse events for nonsupplemented patients. Three reports of fever among nonsupplemented patients included two events reported verbatim as febrile neutropenia, and one event reported as fever. The three reports of leukopenia included two events reported verbatim as neutropenia, and one reported as leukopenia with associated neutropenia.

Three supplemented and 4 nonsupplemented patients had adverse events that resulted in their discontinuation of treatment and study withdrawal. These events included arthralgia, deafness and elevated creatinine levels for the supplemented patients and cerebrovascular accident, dyspnea, abnormal kidney function, and stomatitis for the nonsupplemented patients.

Two patients died during the treatment phase (Cycle 1) of the study, and two additional deaths were reported within 30 days of administration of the last dose of the study drug. These deaths were attributed to disease progression.

The data showed that patients receiving low- dose folic acid and vitamin B_{12} for supplementation in this setting were able to receive more Alimta therapy. Supplemented patients had an improved safety profile with a lower incidence of hematologic toxicity, particularly grade 3 and grade 4 neutropenia and leucopenia but not with nonlaboratory toxicities. However, the relatively small number of patients included in these analyses precluded any firm conclusions on toxicity observations.

Safety Data from Phase 2 and 3 Single-Agent Alimta Studies

For all studies, the objective relating to patient safety was to characterize the qualitative and quantitative toxicities of Alimta, 500 mg/ m2 administered once every 21 days. Patients received prophylactic dexamethasone and folic acid and vitamin B_{12} supplementation. Dose adjustments and delays were allowed based on laboratory and nonlaboratory toxicities.

The original integrated analysis of 207 supplemented patients from single- agent Alimta studies submitted in the Integrated Summary of Safety (ISS) included data from four studies: H3E- MC- JMBT, H3E- MC- JMDM, H3E- MC- JMDR, and H3E- MC- JMDS. These studies were completed at the time the ISS was created. The subsequent analysis included two new studies: H3E- MC- JMEI, which was complete; and H3E- MC- JMEU, which was ongoing. Both of these studies began after the implementation of vitamin supplementation; therefore, all patients in these two studies are supplemented.

Data are presented for the subsequent analysis, followed by the data presented in the ISS on the 207 supplemented patients for comparison.

Table 7.32 summarizes other key aspects of the studies discussed in this section.

Table 7.32. Studies of Alimta as a Single Agent (n= 517)

Study	Tumor Type	Prior Therapy	N[a]	Max. Cycles[b]
JMEI	NSCLC	At least one prior chemotherapy regimen	265	NS
JMBT[c]	Breast	Prior anthracycline or anthracenedione and a taxane required	43	NS
JMDM[c]	Breast	JMBT requirements plus capecitabine	60	NS
JMDR[c]	MPM	None	43	6[d]
JMDS	Breast	None	61	3[e]
JMEU	Bladder	One prior regimen	45	NS

Abbreviations: MPM = malignant pleural mesothelioma; NS = not specified.

a N = number of supplemented patients who received at least one dose of LY231514.

b Maximum number of cycles allowed if there was no evidence of disease progression or unacceptable toxicity, and if the physician and patient agreed it was in the patient's best interest to continue.

c These studies had additional patients who did not receive supplementation.

d More cycles were allowed if the patient was experiencing a clinical benefit.

e Only three cycles were given. Patients then underwent local therapy.

Source: Safety Update. Applicant Table 4.1.

Among the 517 patients who received Alimta as a single agent at a dose of 500 mg/ m^2 every 21 days, with dexamethasone treatment and folic acid and vitamin B_{12} supplementation, the most common reasons for discontinuation were disease progression and completion of protocol-allowed therapy. Because JMEU is an ongoing study with patients still on study and not all data available, a complete account of the reasons for discontinuation from the study was not provided by the sponsors. Twenty- six (26) of the 517 patients (5.0%) discontinued because of adverse events, compared with 3.9% in the ISS database. Nine patients discontinued because of death (excluding study disease- related; 1.7%) and 1 additional patient because of death from study drug toxicity (0.2%), compared with 0.5% (1 patient) because of death (not study disease-related or study drug- related) in the ISS database. Some of these differences could be because of the overall poorer health and poorer prognoses of bladder cancer and previously treated NSCLC patients. However, the overall pattern of reasons for discontinuation was similar to that reported in the ISS.

Only 29 dose reductions were reported of the 2246 doses of Alimta given (1.3%). Thrombocytopenia was the most common reason for dose reduction. Most reductions occurred in Cycle 2 or 3. These results are comparable with those previously reported in the ISS, where 1.2%

of 893 doses of Alimta were reduced; again, thrombocytopenia was most common reason for dose reduction in that database.

Scheduling conflicts accounted for 81% of the 436 dose delays reported. Eighty- four delays were for clinical reasons. The most common clinical reasons for delay were decreased creatinine clearance, respiratory infections (including pneumonia), fatigue, and neutropenia . In the ISS database, fatigue and neutropenia were the most common clinical reasons for dose delay. The large number of patients (265) with previously treated NSCLC, more than 90% of whom had been treated with a platinum- based regimen, may account for the increased reporting of decreased creatinine clearance resulting in dose delay.

Most patients (96.1%) had at least one treatment- emergent adverse event (TEAE), with 82.4% of patients having at least one TEAE considered at least remotely related to study therapy. The most common TEAEs, regardless of causality, were nausea, fatigue, anorexia, and vomiting. The most common drug- related TEAEs were nausea, fatigue, vomiting, and anorexia.

One hundred fifty- nine (159) of the 517 patients (30.8%) experienced one or more of 361 serious adverse events (SAEs), regardless of drug causality. Of these, only 89 SAEs in 48 (9.3%) patients were considered at least remotely related to study therapy. Each of these related SAEs occurred in less than 2% of the patients. The frequencies and patterns of all SAEs and study drug- related SAEs are similar to those reported in the ISS.

As of 18 April 2003, 34 patients who received Alimta on Study JMEI and Study JMEU died while on- study or within 30 days of discontinuing study therapy . Of these, 3 patients from Study JMEI died of study drug- related causes (cardiac arrest, hepatic failure, and pneumonia/ sepsis). All 3 patients from JMEU died because of study disease.

Only 18 of 310 patients (5.8%) in Study JMEI and Study JMEU who received Alimta discontinued study therapy because of an adverse event as of 18 April 2003. All patients were from Study JMEI. Seven of the patients discontinued because of events considered related to study therapy. Events related to renal function were the most common drug- related cause for discontinuation.

Ten serious, unexpected, and reportable adverse events (SURs) were reported in 8 patients who received Alimta in Study JMEI (5 patients) and Study JMEU (3 patients). In Study JMEI, these events were arthralgia and myalgia (both events in the same patient), cytolytic hepatitis (1 patient), pneumonia and sepsis (both events in the same patient), bacterial pneumonia (1 patient), and supraventricular arrhythmia (1 patient). In Study JMEU, the SURs were lower gastrointestinal hemorrhage, hypoglycemia, and migraine (occurring in 1 patient each).

The pattern of CTC laboratory toxicities (Version 2) in the updated safety database was similar to that reported in the ISS database. Grade 3 and 4 transaminase elevations occurred in fewer than 10% of patients. Neutropenia rarely resulted in clinical sequelae; the rate of febrile neutropenia was only 1.9%, very similar to the previously reported rate of 2%.

The pattern of CTC nonlaboratory toxicities (Version 2) in the updated safety database was similar to that reported in the ISS database. Fatigue was the most common grade 3 or 4 toxicity, occurring in 4.7% of patients.

Subgroup analyses of clinically relevant TEAEs showed that decreased creatinine clearance and anemia were reported more commonly in older patients. Anorexia, decreased hemoglobin, and rash occurred significantly more frequently in men, while vomiting and diarrhea occurred more often in women. Analyses of clinically relevant CTC grade 3 and 4 toxicities showed no significant differences between either age or sex subgroups. These results differed slightly from the ISS; however, the conclusion that no particular clinical concern exists for any subgroup remained the same.

The integrated analysis illustrated that the safety profile of single- agent Alimta with folic acid and vitamin B_{12} supplementation and prophylactic dexamethasone was manageable and consistent with increased patient exposure over time. Alimta had predictable toxicities that were mostly mild to moderate, even in patients who had previously received chemotherapy.

Phase 1 Single-Agent Alimta Studies:

Study JMAS

Study JMAS is an Alimta plus folic acid Phase I study which evaluated the maximum tolerated dose of single- agent Alimta administered every 3 weeks, concurrent with two different regimens of supplementation:
- folic acid only, 5 mg oral dose daily for 5 days beginning 2 days before Alimta dose, or
- a multivitamin containing 350 to 600 µg folic acid and vitamin B_{12}, to be taken orally daily.

In addition, there were two cohorts of patients within each vitamin cohort:
- lightly pretreated patients (no prior therapy, 2 courses of mitomycin- C, 6 courses of an alkylating agent, or 4 courses of carboplatin)
- heavily pretreated patients (anything beyond treatments listed above, or radiation to the pelvis).

Planned doses of Alimta could reach 1700 mg/ m^2.

Eighty- seven (87) patients have enrolled in this study as of 18 April 2003.

The most common serious adverse events reported on JMAS thus far, regardless of causality, were neutropenia, vomiting, anemia, nausea, pyrexia, and thrombocytopenia, which were the same as the most common drug-related serious adverse events. Febrile neutropenia occurred in 3.4% of patients thus far.
Two patients experienced severe toxicity during cycle 1. One of these patients was on stable doses of naproxen (500 mg twice per day) concurrent with Alimta at 800 mg/m^2. The other was on stable doses of a long acting NSAID concurrent with 900 mg/m^2 of Alimta.

Only one patient died on- study thus far (of coronary artery disease). No patient deaths had been reported within 30 days of discontinuation of study therapy.
To date, 10 patients had discontinued from Study JMAS because of adverse events.
The serious, unexpected and reportable adverse event of subdural hematoma was reported in one patient. This patient had deep vein thrombosis, was receiving anticoagulants, and also experienced chemotherapy- related thrombocytopenia.
The rate of certain serious adverse events and the rate of discontinuation because of adverse events reported thus far were higher than the rate seen in the Phase 2 and Phase 3 integrated studies. Heavy pretreatment, greater tumor burden, and testing of dose levels of Alimta higher than 500 mg/ m^2 in the study was thought to have contributed to increased rates of certain adverse events and discontinuations because of adverse events.

Reviewers Comment:
In study JMAS, increased toxicity possibly due to the use of NSAIDS with Alimta cannot be excluded.

Study JE-1001

Study JE-1001 was a Phase 1 dose- finding study of single- agent Alimta (plus supplementation and dexamethasone) in Japanese cancer patients. Dose levels to be tested were 300, 500, 600, 700, 800, 900, and 1000 mg/ m^2, with escalation continuing in 100 mg/ m^2- increments, if the listed doses were tolerated. The objective related to safety was to determine the qualitative and quantitative toxicities of this regimen in these patients. Data for this study was not currently in Lilly's database.

Twenty- one (21) patients had enrolled in this study as of 18 April 2003. Eighteen (18) were eligible for safety analyses as of the same date.
As of the data cutoff date, no deaths on study or within 30 days of discontinuation of therapy had been reported.
As of the data cutoff date, no patients discontinued study therapy because of adverse events.
No serious unexpected reportable adverse events had been reported thus far.
The few data available for this ongoing Phase 1 study suggested that therapy was well- tolerated.

4. Adequacy of Safety Testing

The safety population in the randomized trial (study JMCH) represents a population of chemo-naïve patients with MPM, ranging in age from 19-85, average age 60 years, who received Alimta together with cisplatin. Most patients received folic acid and vitamin B_{12} supplementation. Adverse events were more common in the combination treatment group and reduced with vitamin supplementation. The sample of patients is likely to represent the usual MPM patient population. As such, for the specific labeled indication, the safety testing appears appropriate and credible.

5. Summary of Critical Safety Findings and Limitations of Data

This study underwent two distinct stages that evolved because of safety concerns. During the treatment of the first 117 patients, the number of on- study deaths were high. Therefore, an extensive review of the data on these patients and the full safety database of the Alimta development program were done and Lilly decided to add low- dose folic acid and vitamin B_{12} supplementation to all patients. A total of 70 patients had come off study therapy by that date and thus never received the supplementation, while 47 patients continued to receive treatment and were partially supplemented. The decision to add supplementation also resulted in an increase in the sample size as part of a decision to power the subgroup that received supplementation throughout their treatment at the same level as the population in the original design. The results in these supplement-defined subgroups in the safety analyses are of considerable importance because the labeled use is with vitamin supplementation.

Because this was a two- drug versus a one- drug trial, the toxicity of the Alimta/ cisplatin arm was greater than the cisplatin alone control arm as expected.
The frequency of grade 3 and 4 laboratory toxicity was higher in the Alimta/ cisplatin arm when compared to the control arm. The frequency of grade 3/ 4 hematologic toxicity in the fully supplemented Alimta/ cisplatin arm were neutropenia (24.4%), anemia (6%) and thrombocytopenia (5.4%). The uses of colony-stimulating factors were infrequent. Twenty-six patients (15.5%) received RBC transfusions, but platelet and plasma transfusions were infrequent. The frequency of grade 4 toxicity was lower than grade 3 (for neutropenia, 19% Grade 3 versus 5.4% Grade 4). Despite dose reductions and dose delays > 92% of planned doses were delivered.

Nausea, vomiting, and fatigue were the most commonly reported grade 3/ 4 nonlaboratory toxicities in both treatment arms. Nausea and vomiting were more frequent in the Alimta/ cisplatin arm despite the equal frequency of therapy with 5- HT3 antagonists and dexamethasone in the two arms (nausea, 11.3% grade 3 versus 0.6% grade 4).

Supplementation was added to both treatment arms in an effort to maintain blinding of treatment assignments for patients. Analyses by supplementation status were done across treatment arms as well as within treatment arms.
Within the Alimta/ cisplatin arm, supplementation resulted overall in less toxicity, including less grade 3/ 4 toxicity; this was associated with a statistically significant increase in the median number of cycles administered in the fully supplemented subgroup.The frequencies of adverse events were mostly lower in the fully supplemented subgroup when compared to the nonsupplemented subgroup.

Supplementation was also given in the cisplatin alone arm, allowing similar comparisons as in the Alimta/ cisplatin arm. There was a general trend toward fewer adverse events in the fully supplemented subgroup, though the differences were generally less than those seen in the Alimta/ cisplatin arm.

Death rates from all causes while on study drugs between treatment arms were higher in the Alimta/cisplatin group and were reduced with the implementation of supplementation. The FDA review indicated that three deaths in the Alimta/ cisplatin arm could be attributed to be possibly study drug- related, one of which was in the fully supplemented subgroup. There were no study related deaths in the control arm.

The frequencies of discontinuations because of adverse events were low in both arms. Many of the discontinuations in both arms were because of reduced creatinine clearance; the remaining discontinuations thought due to study drugs were distributed over both arms and each had a different cause.

The toxicity profile of Alimta/cisplatin appears consistent with other cytotoxic drugs. The safety population primarily reflects the phase 3 study in chemo-naïve patients.
In this population, Alimta/cisplatin appears to have a high incidence of toxicities that are mostly mild to moderate, even in patients who have received vitamin supplementation.
Adverse events were commonly encountered, suggesting that near maximal dosing was achieved. The toxicities were consistent across the phase 1 and 2 studies done with single –agent Alimta and combination with platinums. Also, most toxicities predicted by the animal studies were confirmed in patients. The adverse event profile of Alimta was judged to be acceptable for patients with MPM. The frequency and severity of adverse events observed during the study were consistent with the clinical course of patients with MPM and with the predicted and known effects of the study drug. Supplemented patients had a better safety profile with a lower incidence of toxicities.

VIII. Dosing, Regimen, and Administration Issues

1. Introduction

The results of the pivotal trial, JMCH, provided confidence in the efficacy and safety of alimta + cisplatin (plus folic acid and vitamin B12) in patients with malignant pleural mesothelioma. However, the underlying science of the addition of folic acid and B12 to an antifolate regimen did not provide confidence with known *in vitro* and *in vivo* antifolate pharmacology. This issue is discussed in detail in section 5 (Important Issues with Pharmacologically Related Agents) of this review.

2. Safety

The recommended dose of Alimta is 500 mg/m^2/dose administered IV over 10 minutes on day 1 with cisplatin in a 21-day cycle. Vitamin supplementation is started prior to starting chemotherapy and continued with treatment. This 21-day cycle is considered a treatment cycle.

Phase 1 studies were conducted exploring three treatment schedules: daily times 5 every 3 weeks (H3E- BP- 001); weekly times 4 every 6 weeks (H3E- MC- JMAB); and once every 3 weeks (H3EMC- JMAA).

Thirty- eight patients were treated at doses ranging from 0.2 to 5.2 mg/ m^2 daily times 5 every 3 weeks in Study BP- 001. The maximum tolerated dose (MTD) was 4 mg/ m^2/ day, with dose limiting toxicities (DLTs) on this schedule of reversible neutropenia and liver enzyme disturbance. Other toxicities included mucositis, diarrhea, rash, fatigue, and elevated transaminases. Minor responses were observed in 2 patients with colorectal and non- small cell lung cancer (NSCLC).

In Study JMAB, 24 patients were treated with a 10-minute infusion of MTA once a week for 4 weeks, with cycles repeated every 6 weeks. Doses ranged from 10 to 40 mg/ m^2/ week. The DLT was myelosuppression, particularly leukopenia and granulocytopenia. Neutropenia prevented weekly dosing in some patients. Nonhematologic toxicities included mild fatigue, anorexia, and nausea. DLT was observed at 40 mg/ m^2/ week, and the recommended dose for Phase 2 evaluation was 30 mg/ m^2/ week. The weekly schedule was not pursued in Phase 2 trials.

In Study JMAA, MTA was administered to 37 patients as a 10-minute infusion once every 3 weeks at doses ranging from 50 to 700 mg/ m^2. The DLTs on this schedule were neutropenia, thrombocytopenia, and fatigue. Of the 20 patients treated at 600 mg/ m^2, Common Toxicity Criteria (CTC) grade 4 neutropenia and grade 4 thrombocytopenia occurred in 4 and 1 patients, respectively, during the first cycle. Grade 2 toxicities at that dose level included rash, mucositis, nausea, vomiting, fatigue, anorexia, and elevations of liver transaminases. Ten patients who developed rashes received dexamethasone 4 mg

twice daily for 3 days starting 1 day prior to treatment with MTA which improved or prevented the rash during subsequent cycles of therapy. There was evidence of cumulative toxicities of neutropenia, thrombocytopenia, and mucositis which may have been due to the prolonged intracellular half- life of the polyglutamate of MTA and decreasing renal function over time with decreased renal drug clearance. Based on this study, the recommended dose for Phase 2 studies was 600 mg/ m^2. Partial responses were observed in two patients with pancreatic cancer and two patients with advanced colorectal cancer. Three of the 4 patients with partial responses had failed previous treatment with thymidylate synthase inhibitors including either 5- FU, FUDR, or raltitrexed.

In a Canadian study in metastatic colorectal cancer, the starting dose of 600 mg/ m^2 was reduced to 500 mg/ m^2 after dose reductions were required in 5 of the first 8 patients. Toxicities leading to these reductions included rash, mucositis, neutropenia, and febrile neutropenia. Responses were seen at this reduced dose in 5 patients for an overall response rate of 17% (95% CI: 6 to 36%). In a US colorectal study, objective tumor responses were seen in 6 of 40 patients for an overall response rate of 15% (95% CI: 6 to 31%).

A multi- institutional study in NSCLC completed in Canada used the lower starting dose of 500 mg/ m^2, which was reduced from 600 mg/ m^2 during the course of the study after 1 of the first 3 patients experienced grade 3 mucositis and grade 4 vomiting and myalgia. Seven partial responses were observed in 30 evaluable patients for an overall response rate of 23.3% (95% CI 9.9 to 42.3%). All responding patients were treated at the 500 mg/ m^2 dose level.

A total of 646 patients were treated on the once every 3 weeks schedule in the Phase 2 setting at 600 mg/ m^2. The most frequent, serious toxicity was hematologic in nature. Grade 3 and 4 hematologic toxicity included neutropenia (23% and 24%, respectively) and thrombocytopenia (7% and 5%, respectively). Although severe neutropenia was common, the frequency of serious infection was low (CTC Grade 4 infection 2%). Likewise, thrombocytopenia had been apparent, and yet serious episodes of bleeding were rare (< 1%). While 6% of patients experienced CTC Grade 3 (5% with Grade 4) skin rash, prophylactic dexamethasone was reported to ameliorate or prevent the rash in subsequent cycles. Other grade 3 and 4 nonhematologic toxicities included stomatitis, diarrhea, vomiting, and infection. Transient grade 3 and 4 elevation of liver transaminases were common but not dose- limiting. There were no cases of persistent transaminase elevation.

Toxicity at 600 mg/ m^2 was recently compared to that at 500 mg/ m^2. For hematologic parameters there appeared to be no difference between the incidence of grade 3 and 4 toxicity or grade 4 toxicity alone. For nonhematologic parameters rash, fatigue, and stomatitis appeared to be less severe at 600 mg/ m^2. Of note, patients who were administered Alimta 500 mg/ m^2 in previous trials had received concomitant dexamethasone after the onset of toxicity, whereas patients at the 600 mg/ m^2 dose level

were given dexamethasone prophylactically. The reduced toxicity profile at the 600 mg/m^2 dose level was thus likely a result of concomitant corticosteroid administration, and was not considered a dose response effect of Alimta treatment.

Because of toxicities seen in two Phase 2 studies (H3E- MC- JMAN and H3E-MCJMAO), the dose of Alimta used in these two studies was reduced from 600 mg/ m^2 to 500 mg/ m^2. With little evidence that a 600 mg/ m^2 dose had an efficacy advantage over a 500 mg/ m^2 dose, the 500 mg/m^2 dose was used in all subsequent single- agent Phase 2 Alimta studies. This decision was made after a discussion with the FDA in September of 1998.

In a Phase 1 trial of Alimta in combination with cisplatin, patients with solid tumors were enrolled into one of two cohorts. The first cohort received both Alimta and cisplatin on Day 1 of a 21- day cycle, and the second cohort received Alimta on Day 1 and cisplatin on Day 2 of a 21- day cycle. Forty patients were enrolled into the first cohort; the MTD was reached at 600 mg/ m^2 MTA and 100 mg/ m^2 cisplatin, with dose- limiting toxicities of thrombocytopenia and febrile neutropenia. Eleven patients were enrolled into the second cohort. The degree of toxicity seen using the split schedule, which included two therapy- related deaths, led to the conclusion that the second schedule was clinically inferior.

Early clinical trials of Alimta recommended the use of dexamethasone as secondary prophylaxis, that is, as pretreatment in future cycles of Alimta after patients experienced troublesome skin rash. After many patients required this secondary prophylaxis, a programmatic decision was made to recommend the use of dexamethasone as primary prophylaxis. A minimum of 3 days of dexamethasone therapy or clinical equivalent was required, but additional days of therapy were allowed as antiemetic prophylaxis.

Pretreatment homocysteine levels significantly predicted severe thrombocytopenia and neutropenia with or without associated grade 3/ 4 diarrhea, mucositis, or infection. Patients with elevated baseline levels of homocysteine alone, or of both homocysteine and methylmalonic acid, were found to have a high risk of severe toxicity. These findings formed the basis to postulate that reducing homocysteine would result in a reduction of severe toxicity. Another finding was that baseline homocysteine levels behaved as a continuous risk factor for toxicity. In addition, no homocysteine level could be identified below which the risk of severe toxicity was low enough to not recommend supplementation. As a consequence, even some patients with normal or near- normal homocysteine levels could have been at an increased risk and, therefore, could benefit from supplementation. It was thus decided to add folic acid and vitamin B_{12} supplementation to all patients receiving Alimta to minimize the risk of severe toxicity.

IX. Use in Special Populations

Table 9.1 summarizes the categories of subgroups analyzed for clinically significant safety variables. CTC toxicities were evaluated by gender and age. There were insufficient numbers of minority patients to evaluate toxicity by race.

Table 9.1. Categorization of Subgroups RT Population

Subgroup	Category	LY cis (N=226)	Cisplatin (N=222)	Total (N=448)
Gender	Female	42	41	83
	Male	184	181	365
Age	<65 Years	143	136	279
	≥65 Years	83	86	169

Source: Section 2.6. Applicant table JMCH.12.49.

1. Evaluation of Sponsor's Gender Effects Analyses and Adequacy of Investigation

1.1 FDA's Efficacy Analyses for Gender Effects

GROUP	ALIMTA/CISPLATIN SURVIVAL, MEDIAN	CISPLATIN ALONE SURVIVAL, MEDIAN	p-value log-rank
Gender Female Randomized and treated (n=83)	15.7 months	7.5 months	0.012
Gender Female Fully folic acid/vitamin B12 supplemented (n=61)	18.9 months	7.4 months	0.01
Gender Male Randomized and treated (n=365)	11 months	9.4 months	0.176
Gender Male Fully folic acid/vitamin B12 supplemented (n=270)	12.8 months	10.4	0.388

The under-powered female subgroup demonstrated in randomized and treated and the fully folic acid/vitamin B12 supplemented groups a statistically significant survival advantage in

favor of the alimta/cisplatin; a similar analysis in the much larger male subgroup demonstrated only trends in favor of the alimta/cisplatin arm.[192]

1.2 Evaluation of Gender Effects on Safety

Each summary represents the proportion of patients with specific treatment- emergent adverse event without regard to relationship to drug and pairwise comparisons within each subgroup strata.

Table 9.2 is a summary of the subgroup analysis for TEAEs by gender. A statistically significant subgroup- by- treatment interaction was observed in rash (p= 0.025). Male patients in the Alimta/ cisplatin group demonstrated a greater frequency of events when compared with males in the cisplatin alone treatment arm. However, events reported for female patients occurred at similar frequencies among treatment groups.

Table 9.2. Summary of Subgroup Analysis for TEAEs by Gender

Event	Subgroup	Subcategory	Therapy	N (%)	Therapy p-value	Interaction p-value
Nausea	Gender	Female	LY/cis	34 (81.0%)	0.592	0.153
			Cisplatin	35 (85.4)		
		Male	LY/cis	156 (84.8)	0.022	
			Cisplatin	136 (75.1)		
Rash NOS	Gender	Female	LY/cis	6 (14.3)	0.964	0.025
			Cisplatin	6 (14.6)		
		Male	LY/cis	52 (28.3)	<0.001	
			Cisplatin	14 (7.7)		
WBC count decreased	Gender	Female	LY/cis	20 (47.6)	0.053	0.058
			Cisplatin	11 (26.8)		
		Male	LY/cis	109 (59.2)	<0.001	
			Cisplatin	32 (17.7)		

Source: Section12.6. Applicant table JMCH.12.50.

Table 9.3 is a summary of the CTC toxicities for the Alimta/cisplatin treatment group by gender. The sample sizes between the two sex subgroups are imbalanced. Caution should be taken when interpreting the results of the analysis. There were no statistically significant differences between the genders for events.

[192] Lilly did a multifactorial survival analysis considering prognostic factors and there was no gender effect; ISE document submitted 3/24/2003.

Table 9.3. Analysis of CTC toxicities for the Alimta/cisplatin Group by Gender (Reviewers Table)

Events	All Grades				Grades 3/4			
	Female		Male		Female		Male	
	N	%	N	%	N	%	N	%
Neutrophils/granulocytes	21	65.6	75	55.1	9	28.1	32	23.5
Hypertension	10	31.3	34	25.0	6	18.8	13	9.6
Vomiting	23	71.9	76	55.9	6	18.8	12	8.8
Nausea	29	90.6	113	83.1	5	15.6	15	11.0
Chest pain	18	56.3	50	36.8	5	15.6	9	6.6
Leukocytes	16	50.0	76	55.9	4	12.5	22	16.2
Fatigue	26	81.3	111	81.6	3	9.4	26	19.1
Dyspnea	17	53.1	93	68.4	3	9.4	16	11.8
Diarrhea without colostomy	11	34.4	32	23.5	3	9.4	3	2.2
Hemoglobin	13	40.6	44	32.4	2	6.3	8	5.9
Tumor pain	5	15.6	26	19.1	2	6.3	6	4.4
Constipation	16	50.0	62	45.6	2	6.3	4	2.9
Renal/Genitourinary-Other	10	31.3	42	30.9	2	6.3	3	2.2
Constitutional Symptoms-Other	6	18.8	12	8.8	2	6.3	2	1.5
Thrombosis/embolism	1	3.1	11	8.1	1	3.1	9	6.6
Platelets	5	15.6	39	28.7	1	3.1	8	5.9
Dehydration	1	3.1	11	8.1	1	3.1	6	4.4
Pulmonary-Other	4	12.5	30	22.1	1	3.1	4	2.9
Hypokalemia	1	3.1	4	2.9	1	3.1	1	0.7
Hyponatremia	1	3.1	3	2.2	1	3.1	1	0.7
Other auditory/hearing	5	15.6	6	4.4	1	3.1	0	0.0
Cushingoid appearance	1	3.1	0	0.0	1	3.1	0	0.0
Dysmenorrhea	1	3.1	1	0.7	1	3.1	0	0.0
GGT	1	3.1	1	0.7	1	3.1	0	0.0
Hypoxia	1	3.1	0	0.0	1	3.1	0	0.0
Prothrombin time	1	3.1	0	0.0	1	3.1	0	0.0
Urticaria	1	3.1	1	0.7	1	3.1	0	0.0
Stomatitis/pharyngitis	13	40.6	34	25.0	0	0.0	5	3.7
Other pain	6	18.8	20	14.7	0	0.0	5	3.7
Anorexia	12	37.5	47	34.6	0	0.0	4	2.9
Infection without Neutropenia	5	15.6	16	11.8	0	0.0	4	2.9
Other Gastrointestinal	7	21.9	26	19.1	0	0.0	3	2.2

Events	All Grades				Grades 3/4			
	Female		Male		Female		Male	
	N	%	N	%	N	%	N	%
Pleuritic pain	1	3.1	28	20.6	0	0.0	3	2.2
Pleural effusion	0	0.0	6	4.4	0	0.0	3	2.2
Supraventricular arrhythmias	0	0.0	5	3.7	0	0.0	3	2.2
Edema	6	18.8	18	13.2	0	0.0	2	1.5
Other musculoskeletal	4	12.5	10	7.4	0	0.0	2	1.5
Mood alteration-depression	3	9.4	20	14.7	0	0.0	2	1.5
Confusion	1	3.1	4	2.9	0	0.0	2	1.5
Dysphagia, esophagitis, odynophagia	1	3.1	9	6.6	0	0.0	2	1.5
Other cardiovascular/general	1	3.1	18	13.2	0	0.0	2	1.5
Hyperglycemia	0	0.0	8	5.9	0	0.0	2	1.5
Ileus	0	0.0	2	1.5	0	0.0	2	1.5
Infection/Febrile Neutropenia-Other	0	0.0	5	3.7	0	0.0	2	1.5
Other cardiovascular/arrhythmia	0	0.0	4	2.9	0	0.0	2	1.5
Pneumonitis/pulmonary infiltrates	0	0.0	4	2.9	0	0.0	2	1.5
Cough	8	25.0	56	41.2	0	0.0	1	0.7
Headache	6	18.8	15	11.0	0	0.0	1	0.7
Mood alteration-anxiety agitation	5	15.6	17	12.5	0	0.0	1	0.7
Rash/desquamation	5	15.6	32	23.5	0	0.0	1	0.7
Creatinine	4	12.5	22	16.2	0	0.0	1	0.7
Dizziness/lightheadedness	4	12.5	12	8.8	0	0.0	1	0.7
Sweating	4	12.5	20	14.7	0	0.0	1	0.7
Arthralgia	3	9.4	5	3.7	0	0.0	1	0.7
Hypomagnesemia	3	9.4	4	2.9	0	0.0	1	0.7
Dyspepsia/heartburn	2	6.3	18	13.2	0	0.0	1	0.7
Incontinence	1	3.1	1	0.7	0	0.0	1	0.7
Infection with grade 3 or 4 Neutropenia	1	3.1	9	6.6	0	0.0	1	0.7
Neuropathic pain	1	3.1	4	2.9	0	0.0	1	0.7
Other endocrine	1	3.1	11	8.1	0	0.0	1	0.7
Salivary gland changes	1	3.1	2	1.5	0	0.0	1	0.7
Tearing	1	3.1	6	4.4	0	0.0	1	0.7
Adult Respiratory Distress	0	0.0	1	0.7	0	0.0	1	0.7

Events	All Grades				Grades 3/4			
	Female		Male		Female		Male	
	N	%	N	%	N	%	N	%
Syndrome								
Ascites	0	0.0	1	0.7	0	0.0	1	0.7
Blood/Bone Marrow-Other	0	0.0	7	5.1	0	0.0	1	0.7
Depressed level of consciousness	0	0.0	2	1.5	0	0.0	1	0.7
Erectile impotence	0	0.0	3	2.2	0	0.0	1	0.7
Febrile neutropenia	0	0.0	1	0.7	0	0.0	1	0.7
Hepatic enlargement	0	0.0	1	0.7	0	0.0	1	0.7
Hepatic pain	0	0.0	1	0.7	0	0.0	1	0.7
Hypercholesterolemia	0	0.0	7	5.1	0	0.0	1	0.7
Hypophosphatemia	0	0.0	1	0.7	0	0.0	1	0.7
Hypotension	0	0.0	5	3.7	0	0.0	1	0.7
Lymphopenia	0	0.0	1	0.7	0	0.0	1	0.7
Muscle weakness	0	0.0	6	4.4	0	0.0	1	0.7
Neuropathy-motor	0	0.0	5	3.7	0	0.0	1	0.7
Operative injury of vein/artery	0	0.0	1	0.7	0	0.0	1	0.7
Other metabolic/laboratory	0	0.0	7	5.1	0	0.0	1	0.7
Pericardial effusion/pericarditis	0	0.0	2	1.5	0	0.0	1	0.7
Renal failure	0	0.0	4	2.9	0	0.0	1	0.7
Vasovagal episode	0	0.0	1	0.7	0	0.0	1	0.7
Insomnia	7	21.9	21	15.4	0	0.0	0	0.0
Fever	5	15.6	23	16.9	0	0.0	0	0.0
Alopecia	4	12.5	15	11.0	0	0.0	0	0.0
Neuropathy-sensory	4	12.5	25	18.4	0	0.0	0	0.0
SGOT(AST)	4	12.5	10	7.4	0	0.0	0	0.0
Abdominal pain or cramping	3	9.4	10	7.4	0	0.0	0	0.0
Conjunctivitis	3	9.4	9	6.6	0	0.0	0	0.0
Other ocular/visual	3	9.4	7	5.1	0	0.0	0	0.0
Pruritus	3	9.4	3	2.2	0	0.0	0	0.0
Weight loss	3	9.4	29	21.3	0	0.0	0	0.0
Allergic rhinitis	2	6.3	9	6.6	0	0.0	0	0.0
Dysuria	2	6.3	2	1.5	0	0.0	0	0.0
Other Dermatology/Skin	2	6.3	12	8.8	0	0.0	0	0.0
Other neurology	2	6.3	12	8.8	0	0.0	0	0.0
Pigmentation changes	2	6.3	4	2.9	0	0.0	0	0.0

Events	All Grades				Grades 3/4			
	Female		Male		Female		Male	
	N	%	N	%	N	%	N	%
SGPT(ALT)	2	6.3	8	5.9	0	0.0	0	0.0
Taste disturbance	2	6.3	13	9.6	0	0.0	0	0.0
Vaginal bleeding	2	6.3	0	0.0	0	0.0	0	0.0
Weight gain	2	6.3	3	2.2	0	0.0	0	0.0
Alkaline phosphatase	1	3.1	1	0.7	0	0.0	0	0.0
Allergic reaction/hypersenitivity	1	3.1	3	2.2	0	0.0	0	0.0
Bone pain	1	3.1	5	3.7	0	0.0	0	0.0
Bruising	1	3.1	2	1.5	0	0.0	0	0.0
Cardiac-ischemia/infarction	1	3.1	6	4.4	0	0.0	0	0.0
Dry eye	1	3.1	2	1.5	0	0.0	0	0.0
Dry skin	1	3.1	4	2.9	0	0.0	0	0.0
Epistaxis	1	3.1	4	2.9	0	0.0	0	0.0
Gastric ulcer	1	3.1	2	1.5	0	0.0	0	0.0
Glaucoma	1	3.1	2	1.5	0	0.0	0	0.0
Hematuria	1	3.1	0	0.0	0	0.0	0	0.0
Hot flashes/flushes	1	3.1	1	0.7	0	0.0	0	0.0
Hyperkalemia	1	3.1	1	0.7	0	0.0	0	0.0
Hypoalbuminemia	1	3.1	3	2.2	0	0.0	0	0.0
Hypocalcemia	1	3.1	1	0.7	0	0.0	0	0.0
Hypothyroidism	1	3.1	2	1.5	0	0.0	0	0.0
Inner ear/hearing	1	3.1	12	8.8	0	0.0	0	0.0
Memory loss	1	3.1	1	0.7	0	0.0	0	0.0
Middle ear/hearing	1	3.1	0	0.0	0	0.0	0	0.0
Myalgia	1	3.1	6	4.4	0	0.0	0	0.0
Neuropathy-cranial	1	3.1	0	0.0	0	0.0	0	0.0
Nystagmus	1	3.1	1	0.7	0	0.0	0	0.0
Other allergy/immunology	1	3.1	6	4.4	0	0.0	0	0.0
Other hepatic	1	3.1	1	0.7	0	0.0	0	0.0
Palpitations	1	3.1	0	0.0	0	0.0	0	0.0
Radiation recall reaction	1	3.1	0	0.0	0	0.0	0	0.0
Rigors, chills	1	3.1	5	3.7	0	0.0	0	0.0
Secondary Malignancy-Other	1	3.1	0	0.0	0	0.0	0	0.0
Tremor	1	3.1	3	2.2	0	0.0	0	0.0
Urinary frequency/urgency	1	3.1	11	8.1	0	0.0	0	0.0
Vision-blurred vision	1	3.1	1	0.7	0	0.0	0	0.0
Voice	1	3.1	6	4.4	0	0.0	0	0.0

Events	All Grades				Grades 3/4			
	Female		Male		Female		Male	
	N	%	N	%	N	%	N	%
changes/strider/larynx								
Acidosis	0	0.0	1	0.7	0	0.0	0	0.0
Apnea	0	0.0	1	0.7	0	0.0	0	0.0
Arthritis	0	0.0	8	5.9	0	0.0	0	0.0
Bicarbonate	0	0.0	1	0.7	0	0.0	0	0.0
Bilirubin	0	0.0	2	1.5	0	0.0	0	0.0
CNS Cerebrovascular ischemia	0	0.0	1	0.7	0	0.0	0	0.0
Cardiac left ventricular function	0	0.0	1	0.7	0	0.0	0	0.0
Catheter-related infection	0	0.0	1	0.7	0	0.0	0	0.0
Coagulation-Other	0	0.0	2	1.5	0	0.0	0	0.0
Cognitive disturbance/learning problems	0	0.0	1	0.7	0	0.0	0	0.0
Conduction abnormality/A/V heart block	0	0.0	1	0.7	0	0.0	0	0.0
Duodenal ulcer	0	0.0	2	1.5	0	0.0	0	0.0
Earache	0	0.0	1	0.7	0	0.0	0	0.0
Erythema multiforme	0	0.0	3	2.2	0	0.0	0	0.0
Flatulence	0	0.0	3	2.2	0	0.0	0	0.0
Flushing	0	0.0	3	2.2	0	0.0	0	0.0
Gastritis	0	0.0	3	2.2	0	0.0	0	0.0
Gynecomastia	0	0.0	1	0.7	0	0.0	0	0.0
Haptoglobin	0	0.0	1	0.7	0	0.0	0	0.0
Hemolysis	0	0.0	3	2.2	0	0.0	0	0.0
Hemoptysis	0	0.0	2	1.5	0	0.0	0	0.0
Hiccoughs	0	0.0	6	4.4	0	0.0	0	0.0
Hyperuricemia	0	0.0	2	1.5	0	0.0	0	0.0
Hypoglycemia	0	0.0	1	0.7	0	0.0	0	0.0
Injection site reaction	0	0.0	1	0.7	0	0.0	0	0.0
Mouth dryness	0	0.0	5	3.7	0	0.0	0	0.0
Nail changes	0	0.0	1	0.7	0	0.0	0	0.0
Nodal/junctional arrhythmia/dysrhythmia	0	0.0	2	1.5	0	0.0	0	0.0
Other hemorrhage	0	0.0	2	1.5	0	0.0	0	0.0
Other lymphatics	0	0.0	1	0.7	0	0.0	0	0.0
Peripheral arterial ischemia	0	0.0	1	0.7	0	0.0	0	0.0

Events	All Grades				Grades 3/4			
	Female		Male		Female		Male	
	N	%	N	%	N	%	N	%
Phlebitis	0	0.0	1	0.7	0	0.0	0	0.0
Photosensitivity	0	0.0	1	0.7	0	0.0	0	0.0
Pneumothorax	0	0.0	1	0.7	0	0.0	0	0.0
Proctitis	0	0.0	1	0.7	0	0.0	0	0.0
Proteinuria	0	0.0	1	0.7	0	0.0	0	0.0
Pulmonary fibrosis	0	0.0	1	0.7	0	0.0	0	0.0
Pyramidal tract dysfunction	0	0.0	1	0.7	0	0.0	0	0.0
Rectal bleeeding/hematochezia	0	0.0	2	1.5	0	0.0	0	0.0
Sense of smell	0	0.0	1	0.7	0	0.0	0	0.0
Sinus bradycardia	0	0.0	1	0.7	0	0.0	0	0.0
Sinus tachycardia	0	0.0	4	2.9	0	0.0	0	0.0
Syndromes-Other	0	0.0	1	0.7	0	0.0	0	0.0
Transfusion: pRBCs	0	0.0	3	2.2	0	0.0	0	0.0
Urinary retention	0	0.0	1	0.7	0	0.0	0	0.0
Ventricular arrhythmia	0	0.0	1	0.7	0	0.0	0	0.0
Vertigo	0	0.0	2	1.5	0	0.0	0	0.0

2. Evaluation of Evidence for Age, Race, or Ethnicity Effects on Safety or Efficacy

2.1 FDA's Efficacy Analyses for Age and Race

GROUP	ALIMTA/CISPLATIN SURVIVAL, MEDIAN	CISPLATIN ALONE SURVIVAL, MEDIAN	p-value log-rank
Race White Randomized and treated (n=410)	12.2 months	9.3 monts	0.024
Race White Fully folic acid/vitamin B12 supplemented (n=303)	13.3 months	10.2 months	0.026
Race Non-white Randomized and treated (n=38)	9 months	8.4 months	0.715
Race Non-white	8.8 months	9.55 months	0.619

GROUP	ALIMTA/CISPLATIN SURVIVAL, MEDIAN	CISPLATIN ALONE SURVIVAL, MEDIAN	p-value log-rank
Fully folic acid/vitamin B12 supplemented (n=28)			
Age < 65 years Randomized and treated ()n=279)	13.3 months	10.2 months	0.02
Age < 65 years Fully folic acid/vitamin B12 supplemented (n=204)	14.7 months	10.8 months	0.052
Age ≥ 65 years Randomized and treated (n=169)	10 months	7.5 months	0.376
Age ≥ 65 years Fully folic acid/vitamin B12 supplemented (n=127)	12.2 months	8.7 months	0.503

The white subgroup demonstrated, in the randomized and treated and the fully folic acid/vitamin B12 supplemented groups, a statistically significant survival advantage in favor of the alimta/cisplatin; the under-powered non-white group demonstrated a trend in favor of alimta/cisplatin in the randomized and treated group and trend in favor of cisplatin in the fully folic acid/vitamin B12 supplemented group. The age < 65 years subgroup demonstrated, in the randomized and treated and the fully folic acid/vitamin B12 supplemented groups, a survival advantage in favor of the alimta/cisplatin that was statistically significant and marginally significant, respectively. The age ≥ 65 years subgroup demonstrated trends in favor of the alimta/cisplatin arm.

2.2 Evaluation of Evidence for Age Effects on Safety

Table 9.4 is a summary of the subgroup analysis for TEAEs by age. Patients randomized to the Alimta/ cisplatin treatment arm who were ≥ 65 years of age demonstrated a significantly greater frequency of nausea (p= 0.009) when compared with patients on the cisplatin alone arm.

Table 9.4. Summary of Subgroup Analysis for TEAEs by Age

Event	Subgroup	Subcategory	Therapy	N	n (%)	Therapy p-value	Interaction p-value
		≥65	LY/cis	83	72 (86.7%)	0.009	0.053
			Cisplatin	86	60 (69.8)		
		<65	LY/cis	143	118 (82.5)	0.845	
Nausea	Age		Cisplatin	136	111 (81.6)		

Source: Section12.6. Applicant table JMCH.12.51.

Table 9.5 is a summary of the analysis of CTC toxicities in the Alimta/cisplatin group by age. The sample sizes between the two age subgroups were imbalanced, with the majority of patients younger than 65 yrs old. Caution should be taken when interpreting the results of the analysis.

Of the adverse events examined, grade 3/4 leucopenia occurred significantly more often in older patients >65 years.

Table 9.5. Analysis of CTC toxicities in the Alimta/cisplatin group by Age (Reviewers Table)

Events	All Grades				Grades 3/4			
	Age<65		Age>65		Age<65		Age>65	
	N	%	N	%	N	%	N	%
Neutrophils/granulocytes	57	53.3	39	63.9	19	17.8	22	36.1
Nausea	91	85.0	51	83.6	13	12.1	7	11.5
Dyspnea	69	64.5	41	67.2	13	12.1	6	9.8
Vomiting	64	59.8	35	57.4	13	12.1	5	8.2
Fatigue	84	78.5	53	86.9	12	11.2	17	27.9
Chest pain	44	41.1	24	39.3	12	11.2	2	3.3
Leukocytes	52	48.6	40	65.6	8	7.5	18	29.5
Hypertension	21	19.6	23	37.7	8	7.5	11	18.0
Diarrhea without colostomy	25	23.4	18	29.5	5	4.7	1	1.6
Thrombosis/embolism	5	4.7	7	11.5	5	4.7	5	8.2
Hemoglobin	30	28.0	27	44.3	4	3.7	6	9.8
Tumor pain	19	17.8	12	19.7	4	3.7	4	6.6
Dehydration	5	4.7	7	11.5	4	3.7	3	4.9
Constipation	45	42.1	33	54.1	3	2.8	3	4.9
Anorexia	35	32.7	24	39.3	3	2.8	1	1.6
Stomatitis/pharyngitis	31	29.0	16	26.2	3	2.8	2	3.3
Other Gastrointestinal	20	18.7	13	21.3	3	2.8	0	0.0
Pulmonary-Other	16	15.0	18	29.5	3	2.8	2	3.3
Infection without Neutropenia	14	13.1	7	11.5	3	2.8	1	1.6

Events	All Grades				Grades 3/4			
	Age<65		Age>65		Age<65		Age>65	
	N	%	N	%	N	%	N	%
Constitutional Symptoms-Other	10	9.3	8	13.1	3	2.8	1	1.6
Pleural effusion	4	3.7	2	3.3	3	2.8	0	0.0
Other pain	17	15.9	9	14.8	2	1.9	3	4.9
Dysphagia, esophagitis, odynophagia	6	5.6	4	6.6	2	1.9	0	0.0
Hyponatremia	3	2.8	1	1.6	2	1.9	0	0.0
Pneumonitis/pulmonary infiltrates	2	1.9	2	3.3	2	1.9	0	0.0
Renal/Genitourinary-Other	24	22.4	28	45.9	1	0.9	4	6.6
Platelets	17	15.9	27	44.3	1	0.9	8	13.1
Sweating	15	14.0	9	14.8	1	0.9	0	0.0
Edema	14	13.1	10	16.4	1	0.9	1	1.6
Headache	14	13.1	7	11.5	1	0.9	0	0.0
Dyspepsia/heartburn	13	12.1	7	11.5	1	0.9	0	0.0
Pleuritic pain	13	12.1	16	26.2	1	0.9	2	3.3
Mood alteration-anxiety agitation	11	10.3	11	18.0	1	0.9	0	0.0
Mood alteration-depression	11	10.3	12	19.7	1	0.9	1	1.6
Dizziness/lightheadedness	10	9.3	6	9.8	1	0.9	0	0.0
Other musculoskeletal	10	9.3	4	6.6	1	0.9	1	1.6
Other auditory/hearing	9	8.4	2	3.3	1	0.9	0	0.0
Creatinine	8	7.5	18	29.5	1	0.9	0	0.0
Other cardiovascular/general	6	5.6	13	21.3	1	0.9	1	1.6
Other endocrine	5	4.7	7	11.5	1	0.9	0	0.0
Tearing	5	4.7	2	3.3	1	0.9	0	0.0
Hypercholesterolemia	4	3.7	3	4.9	1	0.9	0	0.0
Hypomagnesemia	4	3.7	3	4.9	1	0.9	0	0.0
Muscle weakness	4	3.7	2	3.3	1	0.9	0	0.0
Neuropathic pain	4	3.7	1	1.6	1	0.9	0	0.0
Hyperglycemia	3	2.8	5	8.2	1	0.9	1	1.6
Hypokalemia	3	2.8	2	3.3	1	0.9	1	1.6
Blood/Bone Marrow-Other	2	1.9	5	8.2	1	0.9	0	0.0
GGT	2	1.9	0	0.0	1	0.9	0	0.0

Events	All Grades				Grades 3/4			
	Age<65		Age>65		Age<65		Age>65	
	N	%	N	%	N	%	N	%
Hypotension	2	1.9	3	4.9	1	0.9	0	0.0
Other cardiovascular/arrhythmia	2	1.9	2	3.3	1	0.9	1	1.6
Renal failure	2	1.9	2	3.3	1	0.9	0	0.0
Salivary gland changes	2	1.9	1	1.6	1	0.9	0	0.0
Urticaria	2	1.9	0	0.0	1	0.9	0	0.0
Adult Respiratory Distress Syndrome	1	0.9	0	0.0	1	0.9	0	0.0
Ascites	1	0.9	0	0.0	1	0.9	0	0.0
Cushingoid appearance	1	0.9	0	0.0	1	0.9	0	0.0
Dysmenorrhea	1	0.9	1	1.6	1	0.9	0	0.0
Febrile neutropenia	1	0.9	0	0.0	1	0.9	0	0.0
Hepatic enlargement	1	0.9	0	0.0	1	0.9	0	0.0
Hypophosphatemia	1	0.9	0	0.0	1	0.9	0	0.0
Ileus	1	0.9	1	1.6	1	0.9	1	1.6
Operative injury of vein/artery	1	0.9	0	0.0	1	0.9	0	0.0
Pericardial effusion/pericarditis	1	0.9	1	1.6	1	0.9	0	0.0
Prothrombin time	1	0.9	0	0.0	1	0.9	0	0.0
Supraventricular arrhythmias	1	0.9	4	6.6	1	0.9	2	3.3
Vasovagal episode	1	0.9	0	0.0	1	0.9	0	0.0
Cough	37	34.6	27	44.3	0	0.0	1	1.6
Rash/desquamation	23	21.5	14	23.0	0	0.0	1	1.6
Insomnia	21	19.6	7	11.5	0	0.0	0	0.0
Fever	18	16.8	10	16.4	0	0.0	0	0.0
Neuropathy-sensory	17	15.9	12	19.7	0	0.0	0	0.0
Weight loss	17	15.9	15	24.6	0	0.0	0	0.0
Alopecia	13	12.1	6	9.8	0	0.0	0	0.0
Taste disturbance	10	9.3	5	8.2	0	0.0	0	0.0
Abdominal pain or cramping	8	7.5	5	8.2	0	0.0	0	0.0
Conjunctivitis	8	7.5	4	6.6	0	0.0	0	0.0
Inner ear/hearing	8	7.5	5	8.2	0	0.0	0	0.0
Other Dermatology/Skin	8	7.5	6	9.8	0	0.0	0	0.0
Other neurology	8	7.5	6	9.8	0	0.0	0	0.0
SGOT(AST)	8	7.5	6	9.8	0	0.0	0	0.0
SGPT(ALT)	8	7.5	2	3.3	0	0.0	0	0.0
Other ocular/visual	7	6.5	3	4.9	0	0.0	0	0.0

Events	All Grades				Grades 3/4			
	Age<65		Age>65		Age<65		Age>65	
	N	%	N	%	N	%	N	%
Urinary frequency/urgency	7	6.5	5	8.2	0	0.0	0	0.0
Myalgia	6	5.6	1	1.6	0	0.0	0	0.0
Bone pain	5	4.7	1	1.6	0	0.0	0	0.0
Infection with grade 3 or 4 Neutropenia	5	4.7	5	8.2	0	0.0	1	1.6
Pigmentation changes	5	4.7	1	1.6	0	0.0	0	0.0
Pruritus	5	4.7	1	1.6	0	0.0	0	0.0
Voice changes/stridor/larynx	5	4.7	2	3.3	0	0.0	0	0.0
Weight gain	5	4.7	0	0.0	0	0.0	0	0.0
Hiccoughs	4	3.7	2	3.3	0	0.0	0	0.0
Other allergy/immunology	4	3.7	3	4.9	0	0.0	0	0.0
Other metabolic/laboratory	4	3.7	3	4.9	0	0.0	1	1.6
Allergic rhinitis	3	2.8	8	13.1	0	0.0	0	0.0
Arthritis	3	2.8	5	8.2	0	0.0	0	0.0
Confusion	3	2.8	2	3.3	0	0.0	2	3.3
Dry skin	3	2.8	2	3.3	0	0.0	0	0.0
Epistaxis	3	2.8	2	3.3	0	0.0	0	0.0
Infection/Febrile Neutropenia-Other	3	2.8	2	3.3	0	0.0	2	3.3
Mouth dryness	3	2.8	2	3.3	0	0.0	0	0.0
Neuropathy-motor	3	2.8	2	3.3	0	0.0	1	1.6
Sinus tachycardia	3	2.8	1	1.6	0	0.0	0	0.0
Arthralgia	2	1.9	6	9.8	0	0.0	1	1.6
Cardiac-ischemia/infarction	2	1.9	5	8.2	0	0.0	0	0.0
Dysuria	2	1.9	2	3.3	0	0.0	0	0.0
Erectile impotence	2	1.9	1	1.6	0	0.0	1	1.6
Erythema multiforme	2	1.9	1	1.6	0	0.0	0	0.0
Flatulence	2	1.9	1	1.6	0	0.0	0	0.0
Flushing	2	1.9	1	1.6	0	0.0	0	0.0
Gastric ulcer	2	1.9	1	1.6	0	0.0	0	0.0
Gastritis	2	1.9	1	1.6	0	0.0	0	0.0
Hot flashes/flushes	2	1.9	0	0.0	0	0.0	0	0.0
Hyperuricemia	2	1.9	0	0.0	0	0.0	0	0.0
Hypoalbuminemia	2	1.9	2	3.3	0	0.0	0	0.0
Hypothyroidism	2	1.9	1	1.6	0	0.0	0	0.0
Nystagmus	2	1.9	0	0.0	0	0.0	0	0.0

Events	All Grades				Grades 3/4			
	Age<65		Age>65		Age<65		Age>65	
	N	%	N	%	N	%	N	%
Other hemorrhage	2	1.9	0	0.0	0	0.0	0	0.0
Other hepatic	2	1.9	0	0.0	0	0.0	0	0.0
Rigors, chills	2	1.9	4	6.6	0	0.0	0	0.0
Tremor	2	1.9	2	3.3	0	0.0	0	0.0
Vaginal bleeding	2	1.9	0	0.0	0	0.0	0	0.0
Vertigo	2	1.9	0	0.0	0	0.0	0	0.0
Alkaline phosphatase	1	0.9	1	1.6	0	0.0	0	0.0
Allergic reaction/hypersenitivity	1	0.9	3	4.9	0	0.0	0	0.0
Bruising	1	0.9	2	3.3	0	0.0	0	0.0
CNS Cerebrovascular ischemia	1	0.9	0	0.0	0	0.0	0	0.0
Dry eye	1	0.9	2	3.3	0	0.0	0	0.0
Earache	1	0.9	0	0.0	0	0.0	0	0.0
Hematuria	1	0.9	0	0.0	0	0.0	0	0.0
Hemolysis	1	0.9	2	3.3	0	0.0	0	0.0
Hemoptysis	1	0.9	1	1.6	0	0.0	0	0.0
Hyperkalemia	1	0.9	1	1.6	0	0.0	0	0.0
Hypocalcemia	1	0.9	1	1.6	0	0.0	0	0.0
Incontinence	1	0.9	1	1.6	0	0.0	1	1.6
Injection site reaction	1	0.9	0	0.0	0	0.0	0	0.0
Memory loss	1	0.9	1	1.6	0	0.0	0	0.0
Middle ear/hearing	1	0.9	0	0.0	0	0.0	0	0.0
Nail changes	1	0.9	0	0.0	0	0.0	0	0.0
Neuropathy-cranial	1	0.9	0	0.0	0	0.0	0	0.0
Nodal/junctional arrhythmia/dysrhythmia	1	0.9	1	1.6	0	0.0	0	0.0
Other lymphatics	1	0.9	0	0.0	0	0.0	0	0.0
Photosensitivity	1	0.9	0	0.0	0	0.0	0	0.0
Pneumothorax	1	0.9	0	0.0	0	0.0	0	0.0
Proctitis	1	0.9	0	0.0	0	0.0	0	0.0
Proteinuria	1	0.9	0	0.0	0	0.0	0	0.0
Pulmonary fibrosis	1	0.9	0	0.0	0	0.0	0	0.0
Pyramidal tract dysfunction	1	0.9	0	0.0	0	0.0	0	0.0
Radiation recall reaction	1	0.9	0	0.0	0	0.0	0	0.0
Rectal bleeeding/hematochezia	1	0.9	1	1.6	0	0.0	0	0.0
Secondary Malignancy-Other	1	0.9	0	0.0	0	0.0	0	0.0

Events	All Grades				Grades 3/4			
	Age<65		Age>65		Age<65		Age>65	
	N	%	N	%	N	%	N	%
Sense of smell	1	0.9	0	0.0	0	0.0	0	0.0
Sinus bradycardia	1	0.9	0	0.0	0	0.0	0	0.0
Acidosis	0	0.0	1	1.6	0	0.0	0	0.0
Apnea	0	0.0	1	1.6	0	0.0	0	0.0
Bicarbonate	0	0.0	1	1.6	0	0.0	0	0.0
Bilirubin	0	0.0	2	3.3	0	0.0	0	0.0
Cardiac left ventricular function	0	0.0	1	1.6	0	0.0	0	0.0
Catheter-related infection	0	0.0	1	1.6	0	0.0	0	0.0
Coagulation-Other	0	0.0	2	3.3	0	0.0	0	0.0
Cognitive disturbance/learning problems	0	0.0	1	1.6	0	0.0	0	0.0
Conduction abnormality/A/V heart block	0	0.0	1	1.6	0	0.0	0	0.0
Depressed level of consciousness	0	0.0	2	3.3	0	0.0	1	1.6
Duodenal ulcer	0	0.0	2	3.3	0	0.0	0	0.0
Glaucoma	0	0.0	3	4.9	0	0.0	0	0.0
Gynecomastia	0	0.0	1	1.6	0	0.0	0	0.0
Haptoglobin	0	0.0	1	1.6	0	0.0	0	0.0
Hepatic pain	0	0.0	1	1.6	0	0.0	1	1.6
Hypoglycemia	0	0.0	1	1.6	0	0.0	0	0.0
Hypoxia	0	0.0	1	1.6	0	0.0	1	1.6
Lymphopenia	0	0.0	1	1.6	0	0.0	1	1.6
Palpitations	0	0.0	1	1.6	0	0.0	0	0.0
Peripheral arterial ischemia	0	0.0	1	1.6	0	0.0	0	0.0
Phlebitis	0	0.0	1	1.6	0	0.0	0	0.0
Syndromes-Other	0	0.0	1	1.6	0	0.0	0	0.0
Transfusion: pRBCs	0	0.0	3	4.9	0	0.0	0	0.0
Urinary retention	0	0.0	1	1.6	0	0.0	0	0.0
Ventricular arrhythmia	0	0.0	1	1.6	0	0.0	0	0.0

3. Evaluation of Pediatric Program

There is a full waiver for the mesothelioma indication. The safety of alimta in pediatric patients has not been established. Malignant pleural mesothelioma is a disease of adults.

4. Comments on Data Available or Needed in Other Populations

4.1 Pregnancy and Nursing

As a class, folic acid antimetabolites have been demonstrated to produce manifestations of developmental toxicity such as growth retardation, embryo lethality, and malformations. Alimta was found to be embryo toxic at doses of 10 mg/ kg (30 mg/ m^2) and fetotoxic causing fetal malformations (cleft palate) at doses of 5 mg/ kg (15 mg/ m^2). There are no studies of Alimta in pregnant women. If Alimta is used during pregnancy, or if the patient becomes pregnant while taking Alimta, the patient should be apprised of the potential hazard to the fetus.

As with other anti-folate drugs, there is a potential for serious adverse reactions in nursing infants and nursing should be discontinued if the mother is treated with Alimta.

4.2 Renal, Nonsteroidal Anti-Inflammatory Drugs, and Pleural Effusions

Alimta is eliminated primarily via the renal route. Patients with a creatinine clearance of < 45 ml/min, calculated with the mean body weight by the formula of Cockcroft and Gault, should not receive Alimta.

As with other antifolates, caution should be exercised when concomitant administration of Alimta with nonsteroidal anti-inflammatory drugs are used.

Patients with clinically significant pleural effusions have been excluded in studies performed with Alimta. Before starting treatment, pleural effusions should be drained.

X. Conclusions and Recommendations

1. Conclusions

One single-blind, randomized, controlled trial, demonstrating the efficacy and safety of Alimta in combination with cisplatin for the treatment of malignant pleural mesothelioma patients whose disease is either unresectable or who are not candidates for curative surgery has been submitted and reviewed. The pivotal trial was multicenter with United States and non-US sites. The combination of Alimta plus cisplatin is the first chemotheraupetic regimen to demonstrate a survival benefit in malignant pleural mesothelioma in comparison to a control regimen.

The overall survival analyses of the randomized and treated (RT) and the intent-to-treat populations demonstrated a statistically significant improvement in survival in favor of the alimta/cisplatin arm compared to cisplatin alone. In the fully folic acid/vitamin B12 supplemented group, the alimta/cisplatin arm was favored and was marginally statistically significant. Sixty-seven percent of the patients enrolled on study had pathologically confirmed mesothelioma; in the confirmed mesothelioma subset, survival analyses of the RT and the fully folic acid/vitamin B12 supplemented groups demonstrated a marginally significant survival advantage in favor of the alimta/cisplatin arm. The under-powered female subgroup demonstrated in RT and the fully folic acid/vitamin B12 supplemented groups a statistically significant survival advantage in favor of the alimta/cisplatin; a similar analysis in the much larger male subgroup demonstrated only trends in favor of the alimta/cisplatin arm.[193] The white subgroup demonstrated, in the RT and the fully folic acid/vitamin B12 supplemented groups, a statistically significant survival advantage in favor of the alimta/cisplatin; the under-powered non-white group demonstrated a trend in favor of alimta/cisplatin in the RT group and trend in favor of cisplatin in the fully folic acid/vitamin B12 supplemented group. The age < 65 years subgroup demonstrated, in the RT and the fully folic acid/vitamin B12 supplemented groups, a survival advantage in favor of the alimta/cisplatin that was statistically significant and marginally significant, respectively. The age $\geq$ 65 years subgroup demonstrated trends in favor of the alimta/cisplatin arm.

Alimta in combination with cisplatin has satisfactorily demonstrated a consistent survival advantage compared to cisplatin alone in patients with pleural malignant mesothelioma in a randomized, single-blinded study.

The common grade 3 or grade 4 laboratory toxicities in the RT group treated with Alimta plus cisplatin were neutropenia (28.8%), leucopenia (18.1%), thrombocytopenia (5.8%) and anemia (6.2%). In a subgroup analysis of patients fully supplemented with folic acid + vitamine B12 (FS), the Alimta + cisplatin treated arm had neutropenia (24.4%), leucopenia (15.5%), anemia (6%), thrombocytopenia (5.4%) while the cisplatin only arm had neutropenia (3.1%), leucopenia (0.6%) and decreased creatinine (1%). The common

[193] Lilly did a multifactorial survival analysis considering prognostic factors and there was no gender effect; ISE document submitted 3/24/2003.

nonlaboratory grade 3 and grade 4 adverse events in the RT group treated with Alimta + cisplatin were fatigue (18.1%), nausea (14.6%), vomiting (13.7%), diarrhea (4.9%), dehydration (4.4%), stomatitis (4%), anorexia (3.5%) and rash (1.3%). In the FS group, the patients treated with Alimta + cisplatin had fatigue (17.3%), nausea (11.9%), vomiting (10.7%), dehydration (4.2%), diarrhea (3.6%), stomatitis (3%) and anorexia (2.4%). Supplementation with folic acid + vitamin B12 reduced many of the laboratory and non-laboratory toxicities in comparison to a never supplemented subgroup.

However, the demonstration of the survival benefit is based on only one randomized, control trial which had challenges with regard to pathology confirmation, eligibility based on measurable disease, response evaluation, the addition of folic acid plus vitamin B12 into the ongoing pivotal trial, and financial disclosure. In view that these deficiencies could be the result of bias and affect the survival benefit, replication of the survival benefit in another randomized, controlled trial appears desirable although not required for approval.

2. Recommendations

Based on this review of NDA 21-462, Alimta in combination with cisplatIn is clinically approvable for the treatment of malignant pleural mesothelioma patients whose disease is either unresectable or who are not candidates for curative surgery.

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/s/

Robert White
1/28/04 02:37:20 PM
MEDICAL OFFICER

Maitreyee Hazarika
1/28/04 04:20:46 PM
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John Johnson
1/29/04 09:22:47 AM
MEDICAL OFFICER
See also my Clinical Team Leader Review

MEDICAL OFFICER CONSULTATION

Date: November 13, 2003

To: P. Garvey, Project Manager, HFD-150

From: Sally Seymour, MD
Medical Officer
Division of Pulmonary and Allergy Drug Products (HFD-570)

Through: Eugene Sullivan, MD, FCCP
Medical Team Leader (Acting), DPADP

Badrul Chowdhury, MD, PhD
Director, DPADP

Subject: Consultation regarding pulmonary function in a Phase 3 clinical trial conducted to gain marketing approval of Alimta (pemetrexed)

General Information

NDA #	21-462
Sponsor	Eli Lilly & Company
Protocol	H3E-MC-JMCH (g)
Drug Product	Alimta (pemetrexed)
Request From	Division of Oncology Drug Products (HFD-150)
Materials	Proposed label; Protocol H3E-MC-JMCH(g); Pulmonary function results from trial comparing alimta/cisplatin and cisplatin alone

Background

The Division of Oncology Drug Products consulted the Division of Pulmonary and Allergy Drug Products to comment on [redacted] pulmonary function for alimta (NDA 21-462) in the treatment of patients with malignant pleural mesothelioma whose disease is either unresectable or who were not candidates for curative surgery and who had not received prior chemotherapeutic regimens.

Malignant mesothelioma is a tumor of the pleura or the peritoneum associated with prior exposure to asbestos. The disease is refractory to current therapeutic options and consequently the prognosis is poor with median survival < 18 months.

Alimta is an antifolate that exerts antineoplastic activity by disrupting folate-dependent metabolic processes that are essential for cell replication. The Sponsor conducted a multicenter single-blinded randomized Phase 3 trial of alimta plus cisplatin versus cisplatin alone in patients with malignant pleural mesothelioma. Two hundred twenty-six

patients received alimta plus cisplatin while 222 patients received only cisplatin on day 1 of a 21 day cycle. Six cycles were administered with the option of additional cycles at the discretion of the investigator.

The primary endpoint of the trial was survival. The secondary endpoints pertinent to this consult were pulmonary function tests. Per protocol, the Sponsor chose to measure forced vital capacity (FVC), forced expiratory volume in one second (FEV1) and slow vital capacity (SVC) at baseline and prior to every other treatment cycle. According to the protocol, FVC, SVC and FEV1 were measured using standard apparatus and following ATS or European Respiratory guidelines.

Table 1 and Table 2 summarize the results of the forced vital capacity for the Phase 3 clinical trial. Per the Sponsor's protocol, to be included in the analysis of a particular PFT parameter, a patient must have had data from the baseline period and data from at least one cycle among cycles 2, 4, and 6.

Table 1

Forced Vital Capacity
(Liters, % predicted)
RT Population **

		Alimta/Cisplatin		Cisplatin
Cycle	**N**	**LS Mean**	**N**	**LS Mean**
Baseline	167	2.37 (61.52)	156/155	2.45 (62.12)
Cycle 2	152	2.51 (65.37)	141/139	2.44(63.21)
Cycle 4	117	2.57 (67.11) *	89/88	2.41 (63.44) *
Cycle 6	66	2.55 (67.12) *	54/53	2.33 (60.72) *
Average	167	2.54 (66.53) *	156/155	2.40 (62.45) *

**Randomized & Treated * $p < 0.05$

Table 2

Forced Vital Capacity - Change from Baseline
Liters (% predicted)
RT Population **

		Alimta/Cisplatin		Cisplatin
Cycle	**N**	**LS Mean**	**N**	**LS Mean**
Cycle 2	152	0.08 (2.90)	141/139	0 (0.67)
Cycle 4	117	0.14 (4.62) *	89/88	-0.03 (0.70) *
Cycle 6	66	0.12 (4.57) *	54/53	-0.11 (-2.01) *
Average	167	0.11 (4.03) *	156/155	-0.05 (-0.21) *

**Randomized & Treated * $p < 0.05$

The Sponsor would like to make the following claim in the —— section of the label:

C

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Specific Comments

The Division of Oncology Drug Products has asked the following questions:

1. What are the appropriate pulmonary function tests to demonstrate benefit in this disease?

   Malignant mesothelioma causes a loss of lung volume and therefore would be expected to produce a restrictive pattern on pulmonary function tests. Measurement of lung volumes such as total lung capacity and vital capacity would be the most appropriate variables to monitor a restrictive disease, while FEV1 is less useful. Unless a significant amount of obstruction and/or air trapping is present, the FVC and SVC should be similar and performing analysis on both is redundant. Although the FVC can suggest restriction, it is effort dependent and lung volumes are necessary to confirm the restrictive defect. Therefore, the ideal parameter for assessing restrictive physiology would be lung volume measurements, which can be performed using helium dilution or body plethysmography. However, of the variables the Sponsor measured, the FVC could reasonably be used to monitor and analyze trends. Therefore, the remainder of this consult will focus on the FVC results.

2. What degree of improvement in pulmonary function is clinically important?

   The degree of improvement in pulmonary function that is clinically important is not well defined. Therefore even though the data shows a statistically significant difference between groups in FVC, the clinical relevance of the magnitude of change is unclear.

   When measuring FVC, several acceptable maneuvers are recorded to show reproducibility. According to the American Thoracic Society, the two largest FVCs from acceptable maneuvers can vary up to 200 mL.[1] In addition, serial measurement of FVC is subject to a certain amount of variability often termed the coefficient of variation. The amount of within subject variability is not well defined but is often estimated to be around 5% over the course of day-to-day measurement.[2]

   The Sponsor's data for FVC reported in Table JMCH.11.69 and Table JMCH.11.70 is summarized in Table 1 and Table 2, above. The average mean increase in FVC from baseline in the alimta/cisplatin arm was 110mL while the average mean decrease from baseline in the cisplatin arm was 50mL. Thus, the difference between groups in average mean change in FVC totals 160mL.

[1] Am J Respir Crit Care Med 1995; 152:1107-1136.
[2] Am Rev Respir Dis 1991; 144:1202-1218.

Because the difference between groups in mean change from baseline FVC in this trial is less than the range of variability allowed by the ATS in a single test session and less than generally accepted day-to-day variability, it is the opinion of this Reviewer that the difference in FVC is not clinically significant.

If the effects of multiple cycles of alimta are felt to be cumulative, one could argue that it would be more appropriate to base conclusions on the Cycle 6 data, rather than the data representing the average values over multiple cycles. One difficulty with this approach is that the numbers of patients for which data are available become quite small with successive cycles. That said, the largest change in FVC was in cycle 6 in which the alimta/cisplatin arm showed a mean increase from baseline FVC of 120mL while the cisplatin arm showed a mean decrease from baseline FVC of 110mL. The difference between groups in mean change from baseline FVC was 230mL. Although this is a larger increase in FVC, the value is only slightly out of the range of variability allowed by the ATS in a single test session. In addition, as mentioned above, the significant decline in patient data available during the course of the trial makes any interpretation of the data very difficult. Therefore, it remains the opinion of this Reviewer that the difference in FVC is not clinically significant.

3. Does the data on pulmonary function support the label claims of improvement in pulmonary function

It doesn't appear that appropriate statistical methods were specified to account for multiplicity among the various secondary endpoints. DPADP defers to DODP in regards to whether this alone would preclude inclusion of the proposed claims in the label.

Although the data on pulmonary function does support a statistically significant difference between the two treatment groups (issues of multiplicity aside), the effect size is not considered clinically meaningful

The observation that we see in this study is interesting. To support a specific labeling claim of an improvement in lung function which is clinically meaningful, the Sponsor should do a 'second' trial where assessment of lung function is declared as the primary variable. A 'second' trial is recommended because of the secondary nature of the observation in this trial as well as lack of control of multiplicity. Furthermore, the choice of variables to be measured would need further explanation with a detailed discussion in the protocol of what would constitute a favorable response. Finally, in the design of the 'second' trial, the Sponsor would need to address the significant decline in the numbers

of patients for which data are available, which was noted during the course of this trial.

cc: HFD-570/Sullivan/Medical Team Leader (Acting)
HFD-570/Chowdhury/Division Director
HFD-570/Barnes/Chief Project Management Staff

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